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Living Better Longer:
Influenza vaccination supports healthy aging across the spectrum of frailty

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and Community Health & Epidemiology
Dalhousie University

Disclosure Statement

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I am involved in research grants and funding from industry	GSK, Pfizer, Sanofi with the Canadian Institutes of Health Research, Public Health Agency of Canada and the Canadian Frailty Network	Focus is on frailty, function, VE and outcomes, not product specific
I am currently participating in or have participated in a clinical trial within the past two years	N/A	
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Key Points

1) Frail older adults are at increased risk for influenza and its complications, BUT vaccine effectiveness is lower.
   - If we do not consider frailty in studies of influenza vaccine effectiveness, we underestimate vaccine effectiveness: “frailty bias”
2) The burden of influenza is usually considered over acute time horizons. We need to consider longer term impact of influenza illness and its complications, e.g. persistent functional decline.
3) Older adults may not present with classic symptoms of “influenza like illness”. This has implications for clinical care and surveillance.

So what does frailty have to do with influenza?

Figure credit: Janet McElhaney

The Effect of Immunosenescence

Incidence of serious outcomes of influenza ↑

Most influenza deaths occur in older people

For every influenza death, there are 3–4 influenza hospitalizations (most are ≥65)

Response to vaccination ↓

CURRENT INFLUENZA VACCINE

Effectiveness in preventing respiratory illness is lower in older people than in healthy adults

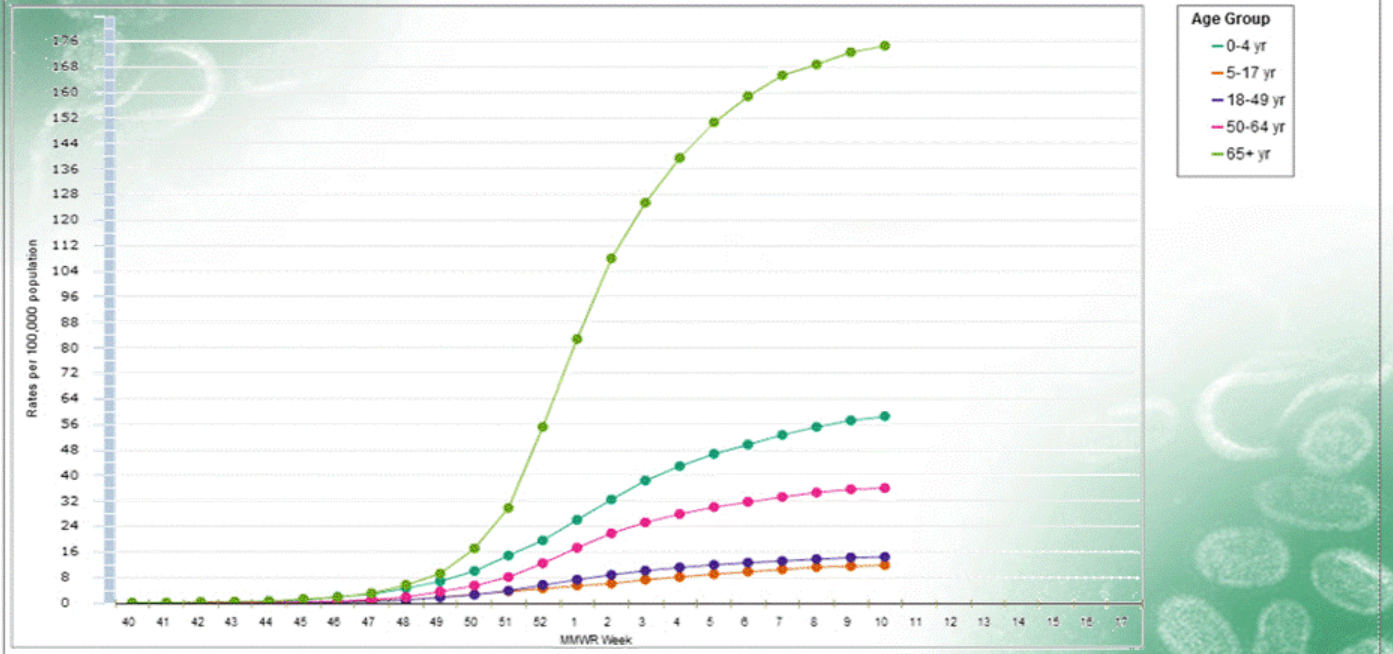
BUT has benefit in prevention of poor outcomes

FLUVIEW

A Weekly Influenza Surveillance Report Prepared by the Influenza Division

Laboratory-Confirmed Influenza Hospitalizations

Preliminary rates as of Mar 09, 2013



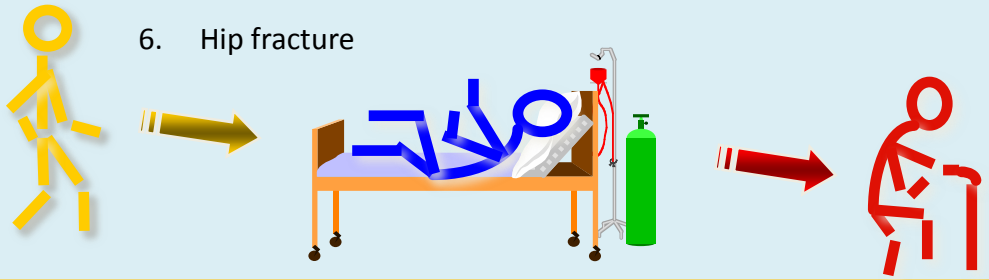
Data from the Influenza Hospitalization Surveillance Network (FluSurv-NET), a population-based surveillance for influenza related hospitalizations in children and adults in 15 US states. Incidence rates are calculated using the National Center for Health Statistics' (NCHS) population estimates for the counties included in the surveillance catchment area.

Vaccine Preventable Disability

Catastrophic disability

- Defined as a loss of independence in ≥ 3 ADL
- 72% who experience catastrophic disability have been hospitalized
- Leading causes of catastrophic disability

1. Strokes
2. CHF
3. Pneumonia and influenza
4. Ischemic heart disease
5. Cancer
6. Hip fracture



Ferrucci et al. JAMA 277:728, 1997
Barker et al. Arch Int Med 158:645, 1998
Falsey et al. *N Engl J Med*. 2005;352:1749

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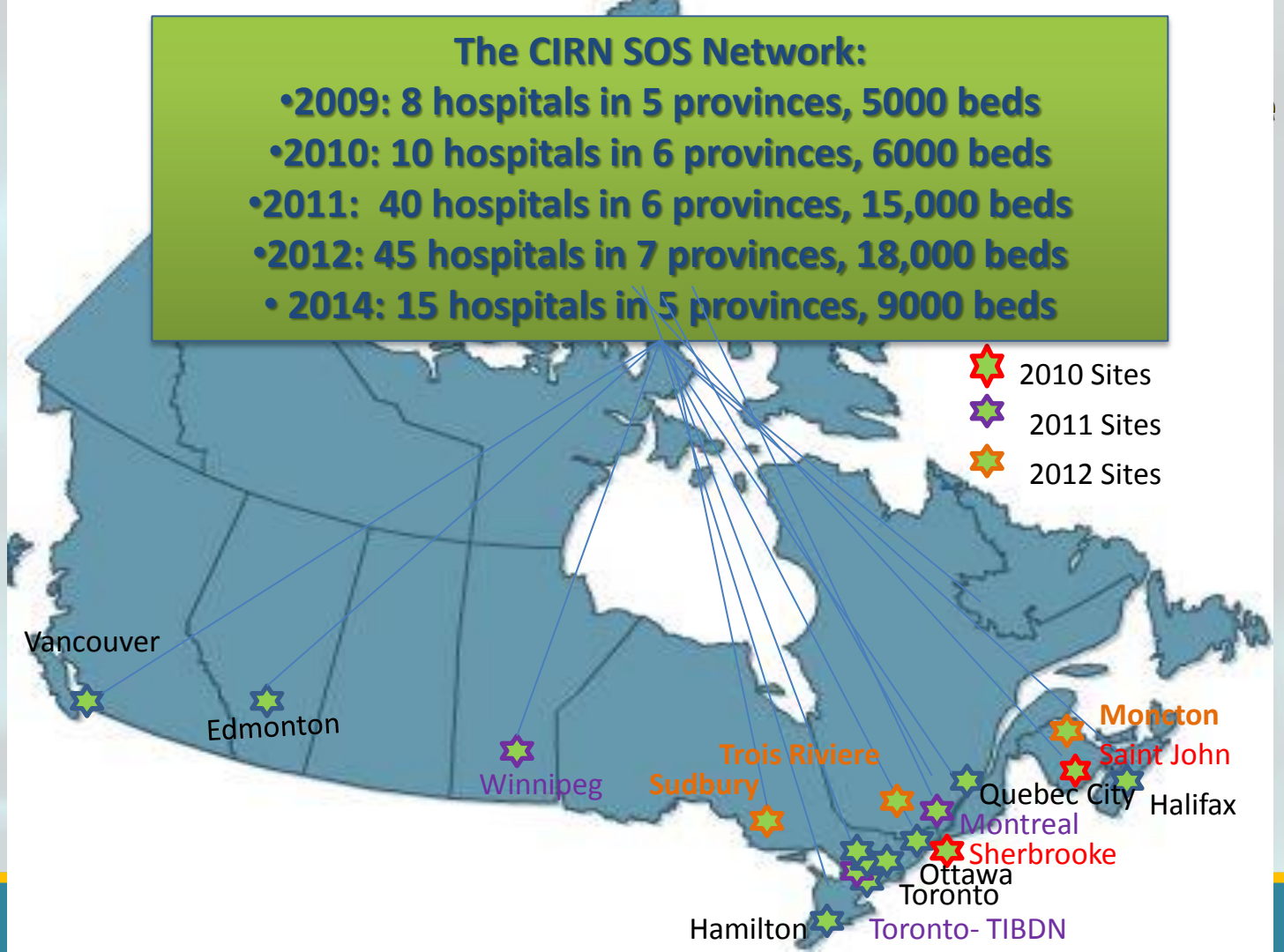

The CIRN SOS Network:
•2009: 8 hospitals in 5 provinces, 5000 beds
•2010: 10 hospitals in 6 provinces, 6000 beds
•2011: 40 hospitals in 6 provinces, 15,000 beds
•2012: 45 hospitals in 7 provinces, 18,000 beds
• 2014: 15 hospitals in 5 provinces, 9000 beds
2010 Sites
2011 Sites
2012 Sites
Vancouver
Edmonton
Winnipeg
Trois Riviere
Sudbury
Moncton
Saint John
Halifax
Quebec City
Montreal
Sherbrooke
Ottawa
Toronto
Hamilton
Toronto- TIBDN

SOS Methods

- Up to 45 sentinel teaching hospitals across Canada
- active surveillance for influenza infection in adults (≥ 16 years of age)
  - NP swab obtained from all patients with an admitting diagnosis of CAP, exacerbation of COPD/asthma, unexplained sepsis, any respiratory diagnosis or symptom OR acute coronary syndrome, stroke or any other cardiac diagnosis with fever (≥37.5˚C)
  - All NP swabs tested for influenza A & B by PCR

Vaccine Effectiveness calculation in a test-negative case control design

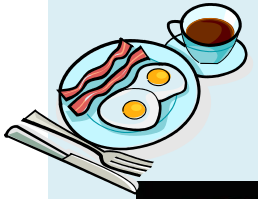
- VE estimated as:

(1-OR of vaccination in cases vs controls)*100

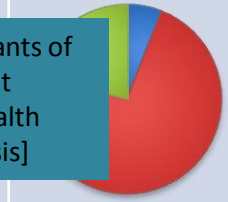
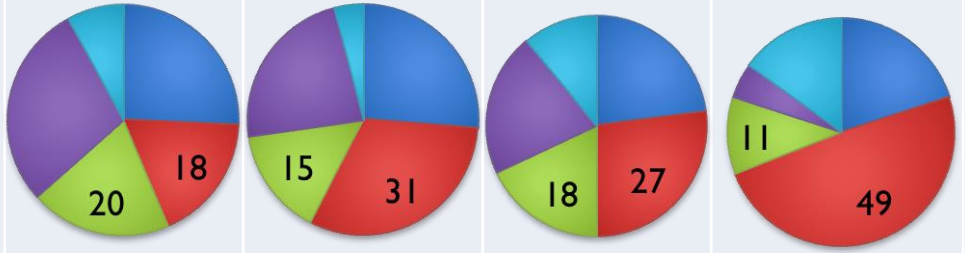
  - Assuming protection from vaccine from 14 days post vaccination
  - Unadjusted & Adjusted (conditional logistic regression with backward stepwise selection; $p \leq 0.1$)
  - Overall VE and VE in age subgroups (16-49y, 50-64y, 65-75y, and >75y)
  - VE by influenza type/subtype
  - Consider health measures and outcomes important for older adults (frailty, function, mobility)

APPENDIX 6: Frailty Index and Frail Scale

Frailty Index (for patients 65 years and older)		Check if Frailty Index was not done: ☐
	Two Weeks Prior to Admission	**On Admission**
A. Cognition	☐ WNL ☐ CIND ☐ Dementia ☐ Delirium due to illness? ☐ unk If dementia, type _____	☐ WNL ☐ CIND ☐ Dementia ☐ Delirium due to illness? ☐ unk If dementia, type _____
C. Mood	☐ WNL ☐ Low mood ☐ Depression ☐ Anxiety ☐ unk	☐ WNL ☐ Low mood ☐ Depression ☐ Anxiety ☐ unk
D. Sensory	Hearing ☐ WNL ☐ Impaired ☐ unk Vision ☐ WNL ☐ Impaired ☐ unk Speech ☐ WNL ☐ Impaired ☐ unk	Hearing ☐ WNL ☐ Impaired ☐ unk Vision ☐ WNL ☐ Impaired ☐ unk Speech ☐ WNL ☐ Impaired ☐ unk
E. Mobility	Transfers ☐ I ☐ A ☐ D ☐ unk Ambulates ☐ I ☐ A ☐ Non-amb ☐ unk Aid ☐ Y ☐ N ☐ unk If yes, aid type: ☐ Cane ☐ 2ww ☐ 4ww ☐ unk Balance ☐ WNL ☐ Impaired ☐ unk Falls ☐ Y ☐ N ☐ unk	Transfers ☐ I ☐ A ☐ D ☐ unk Ambulates ☐ I ☐ A ☐ Non-amb ☐ unk Aid ☐ Y ☐ N ☐ unk If yes, aid type: ☐ Cane ☐ 2ww ☐ 4ww ☐ unk Balance ☐ WNL ☐ Impaired ☐ unk Falls ☐ Y ☐ N ☐ unk
F. Nutrition	Weight ☐ Stable ☐ Loss ☐ Gain ☐ unk	Weight ☐ Stable ☐ Loss ☐ Gain ☐ unk
G. Function	Bathing ☐ I ☐ A ☐ D ☐ unk Toileting ☐ I ☐ A ☐ D ☐ unk Meds ☐ I ☐ A ☐ D ☐ unk Dressing ☐ I ☐ A ☐ D ☐ unk Eating ☐ I ☐ A ☐ D ☐ unk Finances ☐ I ☐ A ☐ D ☐ unk I =Independent , A=Assisted, D =Dependant	Bathing ☐ I ☐ A ☐ D ☐ unk Toileting ☐ I ☐ A ☐ D ☐ unk Meds ☐ I ☐ A ☐ D ☐ unk Dressing ☐ I ☐ A ☐ D ☐ unk Eating ☐ I ☐ A ☐ D ☐ unk Finances ☐ I ☐ A ☐ D ☐ unk I =Independent , A=Assisted, D =Dependant
H. Skin	Ulcers ☐ Y ☐ N ☐ unk Edema ☐ Y ☐ N ☐ unk	Ulcers ☐ Y ☐ N ☐ unk Edema ☐ Y ☐ N ☐ unk
I. Continence (ostomy managed by patient = continent)	Bladder : ☐ Continent ☐ Incontinent ☐ unk Bowel : ☐ Continent ☐ Incontinent ☐ unk	Bladder: ☐ Continent ☐ Incontinent ☐ unk Bowel : ☐ Continent ☐ Incontinent ☐ unk
J. Frailty Scale	1 to 9: _____	1 to 9: _____

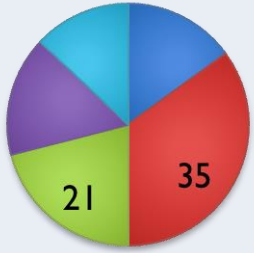
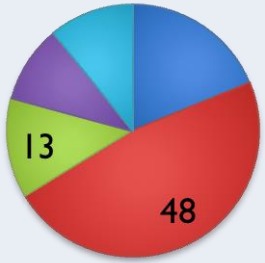
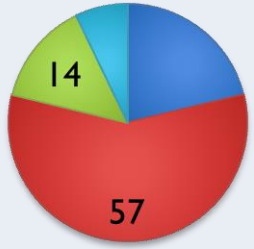


Age and Burden of Disease

	Age 16 – 49 N = 128	Age 50-64 N = 118	Age 65-75 N = 109	Age >75 N = 237
% vaccinated				
BOD by strain				
Death	1 (0.8%)	3 (2.5%)	6 (5.5%)	36 (15.2%)
ICU	16 (12.5%)	20 (16.9%)	17 (15.6%)	22 (9.3%)

M Roy *et al*. Determinants of non-vaccination against seasonal influenza. Health Rep 2018 [CCHS analysis]

Frailty and Burden of Disease

	Low Frailty (FI < 0.2) N = 92	Med Frailty (FI 0.2-0.45) N = 84	High Frailty (FI <0.45) N = 14
% vaccinated			
BOD by strain			
Death	5 (5.4%)	11 (13.1%)	5 (35.7%)
ICU	7 (7.6%)	11 (13.1%)	1 (7.1%)

Frailty impacts Vaccine Effectiveness

(2011/2012) Andrew et al. JID 2017

	Unadjusted (95% CI)	Adjusted (95% CI)
Overall	41.8 (26.0-54.3)	42.8 (23.8-57.0)*
Age < 65y	35.8 (4.5-56.8)	33.2 (-6.7-58.2) †
Age ≥ 65y	45.0 (25.7-59.3)	58.0 (34.2-73.2) ‡

Adjusting for frailty alone very closely approximates the final fully adjusted model. Frailty is the most important confounder to take into account in adults 65+.

*Stepwise l
Obesity, Chi
age, vaccina
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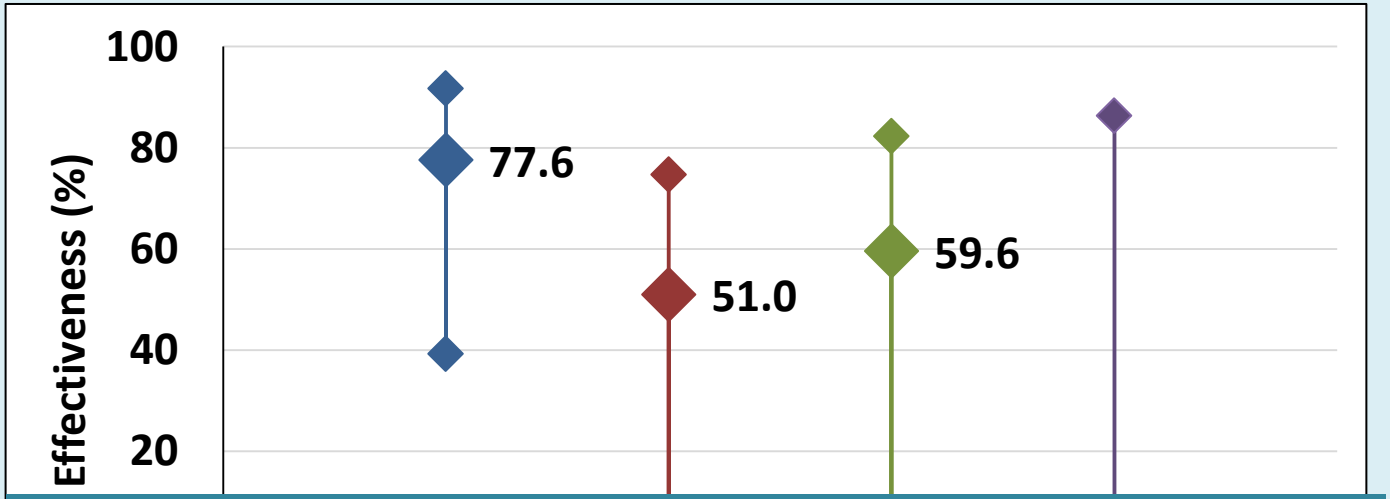
Vaccine Effectiveness decreases as frailty increases*

*Post-Hoc Analysis



Most older adults are not frail (prevalence ~24% in community-dwellers)

BUT the most frail are likely to be at highest risk from influenza and its complications

The problem of BIAS: how do vaccinated and unvaccinated people differ?

- **Bias** is any factor independently associated with risk of disease and vaccination status
  - Healthy user bias- persons more likely to be vaccinated are less likely to develop disease-
    - OVER-estimates VE
  - Indication (frailty) bias- persons more likely to be vaccinated (e.g. frail elderly people) are more likely to have suboptimal vaccine response and experience adverse more influenza outcomes
    - UNDER-estimates VE

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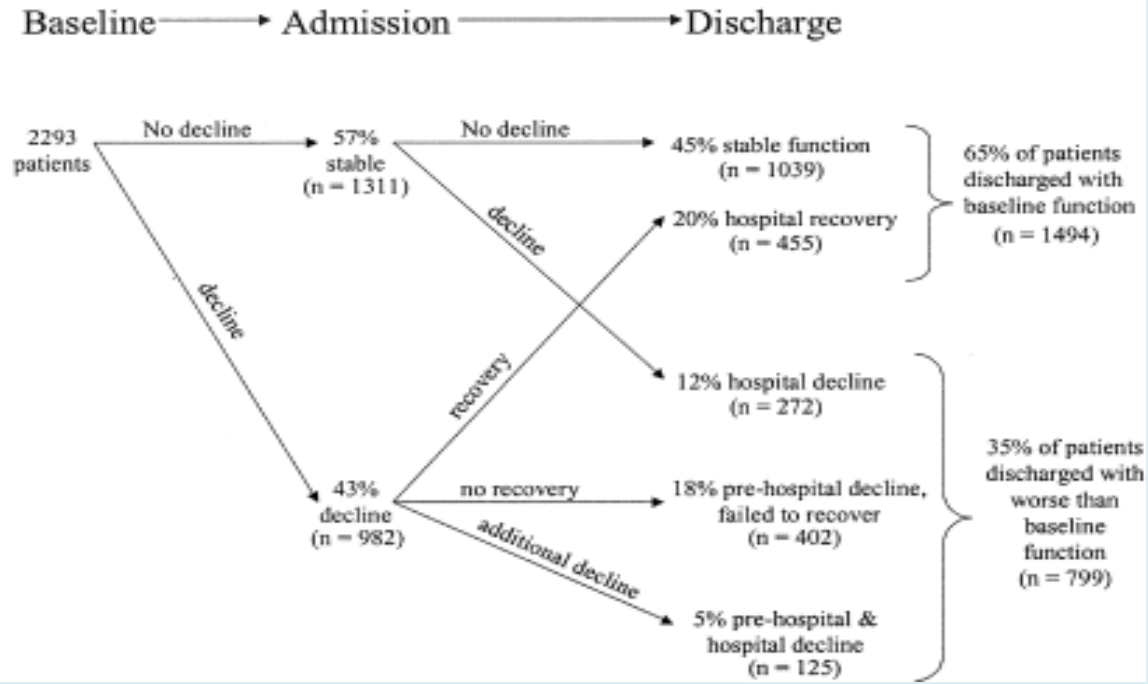
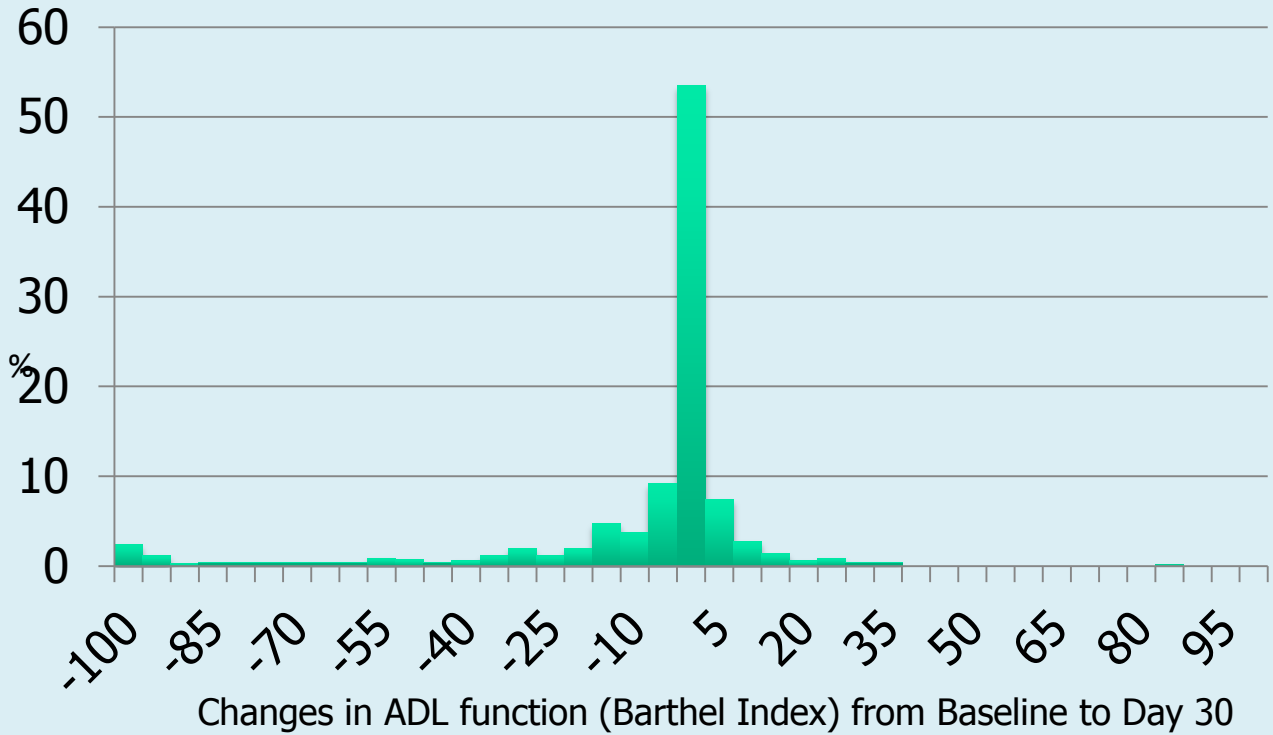
Functional loss is common when older people are in hospital



Covinsky JAGS 2003

Older adults hospitalized with influenza suffer a significant burden of functional decline, which can be persistent



EXACT survey

- 5014 Canadian older adults completed our online survey (March-April 2017) about influenza, vaccine and complications
- Mean age 71.3 ± 5.17 years, 50% were female, and 42.6% had >= 1 chronic conditions
- Clinical Frailty Scale: 7.8% were vulnerable and 1.8% frail
- 68% reported receiving the 2016/17 influenza vaccine
- 21.5% reported having influenza last season
- 20% of these were unable to conduct certain daily activities during the acute illness
- 40% took longer than two weeks to recover
- 3.1% “never fully recovered”
- Older age, memory loss, and having influenza/ILI were among the independent predictors of persistent declines in health and function.

Andrew MK, Gilca V, Waite N, Pereira J. *Ms* submitted 2018
Pereira J, Gilca V, Waite N, Andrew MK. Hum Vacc Immunother 2018

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How well do ILI and SARI criteria perform?

- Influenza-Like Illness
- An acute respiratory Infection with:
  - Measured fever >=38.0 °C
  - And cough
  - With onset within the last 10 days

Sensitivity
65+:
44.6 (43.5-45.8)
No High Risk:
57.0 (52.7-61.4)

- Severe Acute Respiratory Illness
- An acute respiratory infection with:
  - History of fever or measured fever >=38.0 °C
  - And cough
  - With onset within the last 10 days
  - And requires hospitalizati

65+:
57.1
(55.9-58.2)
No High Risk:
70.7
(66.8-74.7)

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So what does frailty have to do with influenza?

Figure credit: Janet McElhaney

Understanding frailty is important in identifying influenza illness and measuring influenza vaccine effectiveness

Understanding the impact of influenza on frailty and function is critical to understanding its true burden

NOT Adding Life to Years

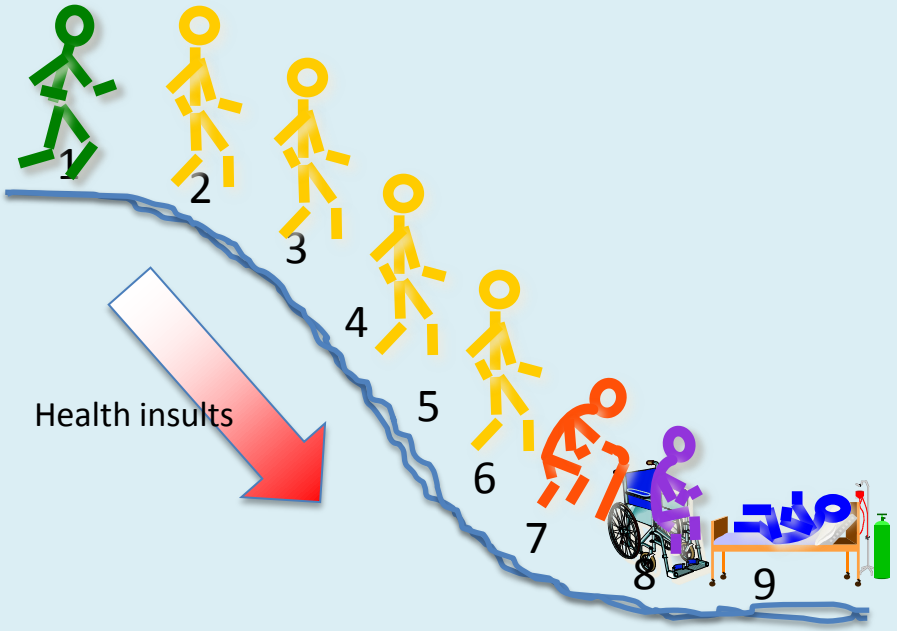
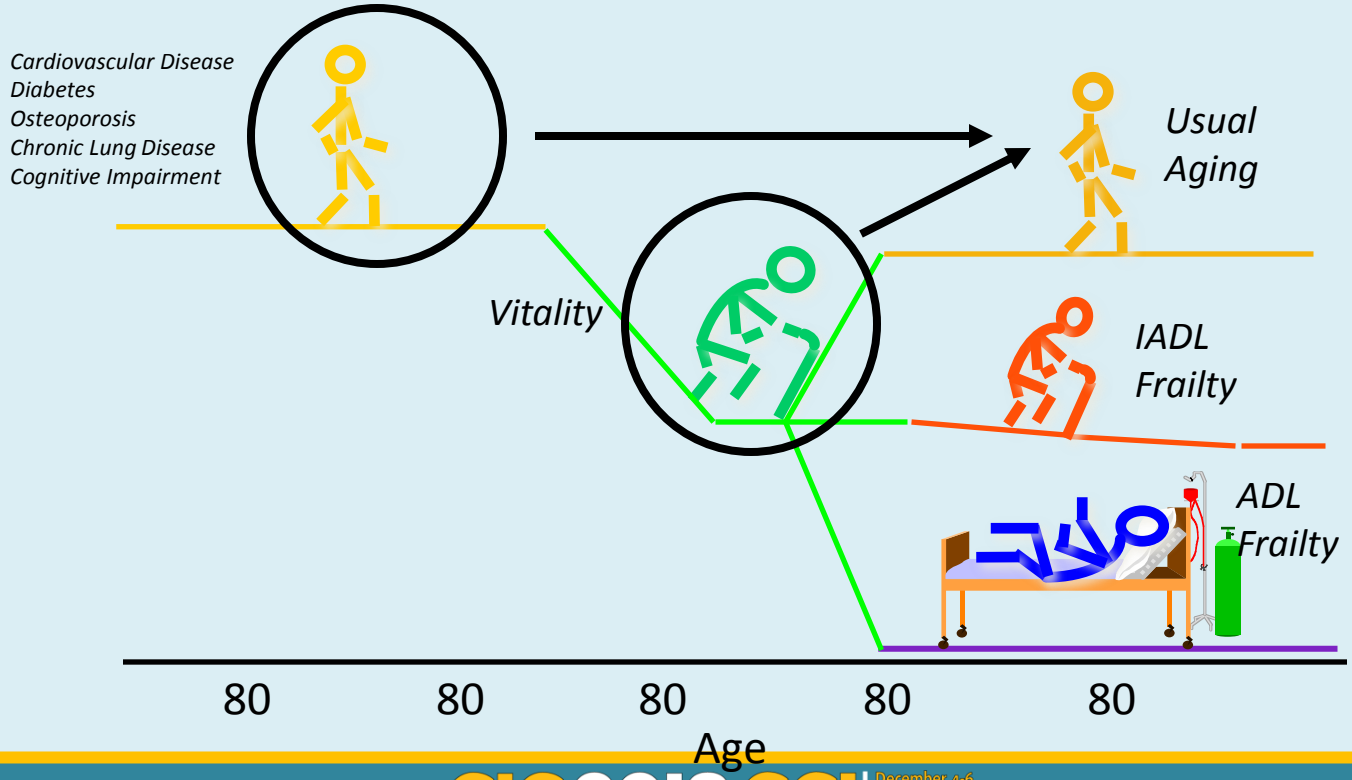


Figure credit: Janet McElhaney

Our aim: Maintenance of function



Adding Life to Years:
Can frailty and disability be prevented?

Candidates:
- Exercise
- Social integration
- Physiological interventions: nutrition, inflammation, immune, drugs?
- Good care?

  * At least we can prevent some consequences and complications of frailty!
  - Avoidable illness & hospitalizations
  - Vaccine preventable illness and disability!

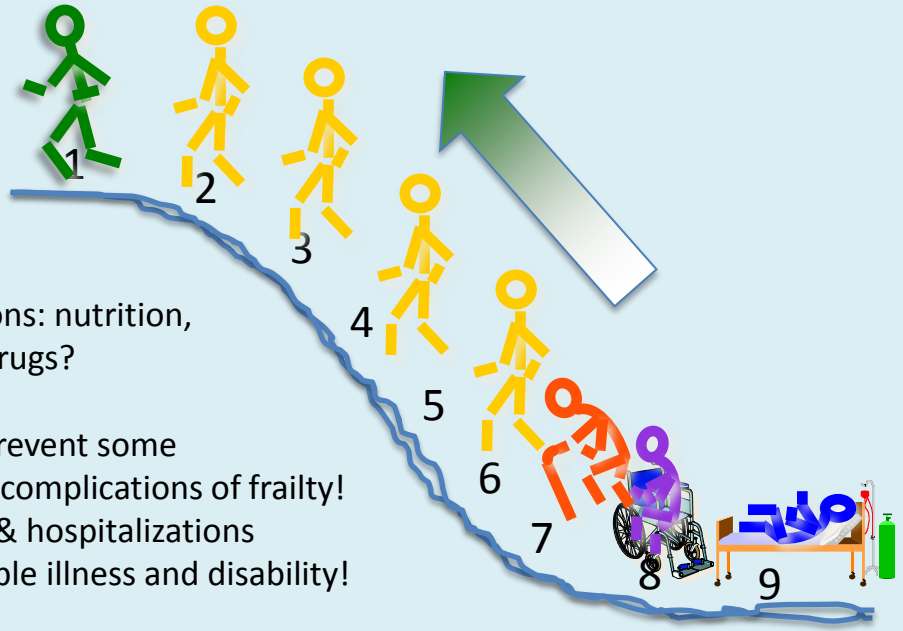


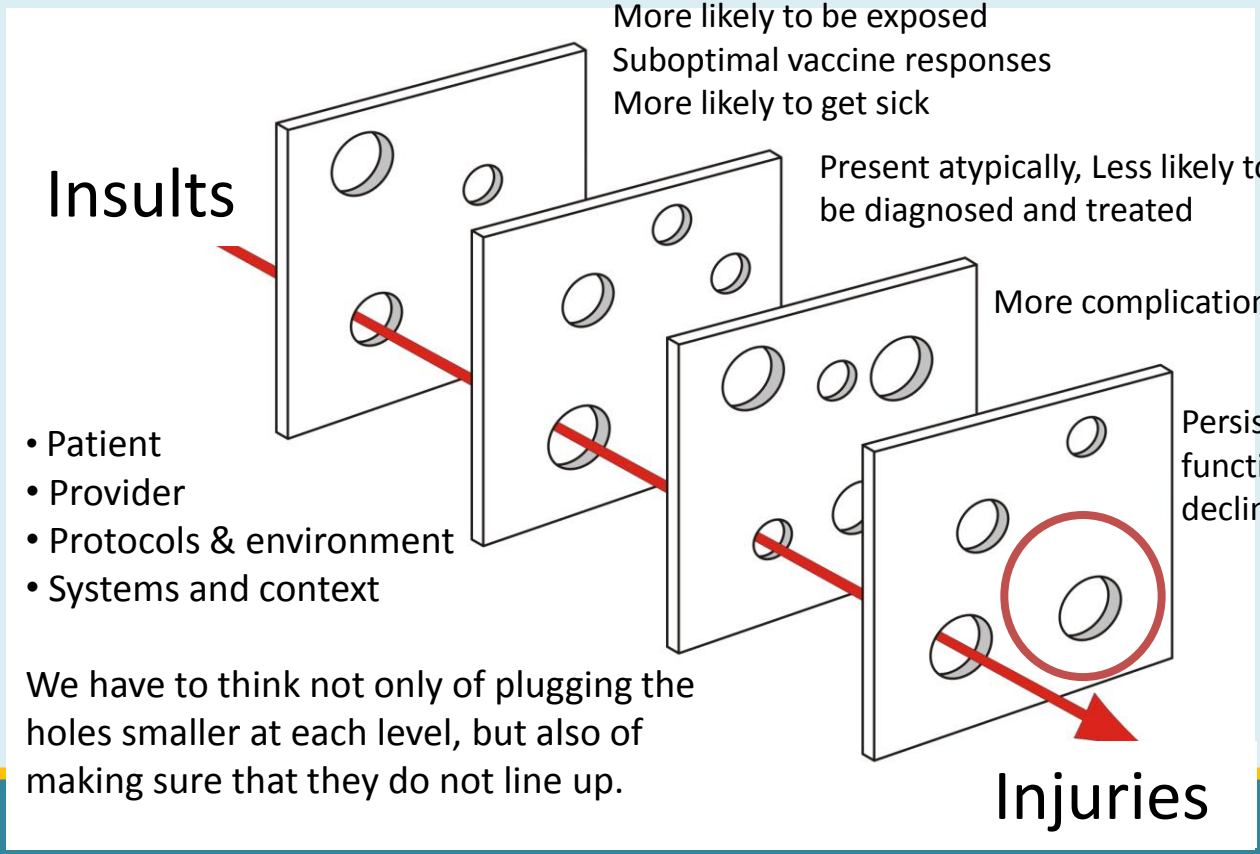
Figure credit: Janet McElhaney

How should this impact practice?

- Actively recommend vaccination for older adults across grades of frailty, establish protocols
- Consider different vaccine products, depending on setting
- Prevent influenza in those around them too
  - Vaccinate family, caregivers, health care professionals
  - Hand hygiene, self-isolate when ill…
- Broaden surveillance and clinical diagnosis and management
  - If we do not look for ‘flu, we will often miss it
- Consider frailty and function in research and clinical practice

Andrew, Bowles, Pawelec, Haynes, Kuchel, McNeil, McElhaney. Influenza vaccination in older adults: recent innovations and practical applications. Drugs & Aging 2018

Putting it all together – improving influenza prevention and care for older adults



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Drugs & Aging review paper collaborators: Susan Bowles, Graham Pawelec, Laura Haynes, George Kuchel, Shelly McNeil, Jan McElhaney

Living better longer: The Role of New Vaccines in Healthy Aging

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Clinician Scientist, Canadian Center for Vaccinology, Dalhousie University

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I am a member of a Speaker's Bureau	N/A	
I am involved in research grants and funding from industry	GSK, Pfizer, Sanofi, Merck	Focus on clinical trials results and NACI recommendations
I am currently participating in or have participated in a clinical trial within the past two years	GSK, Pfizer, Sanofi, Merck	
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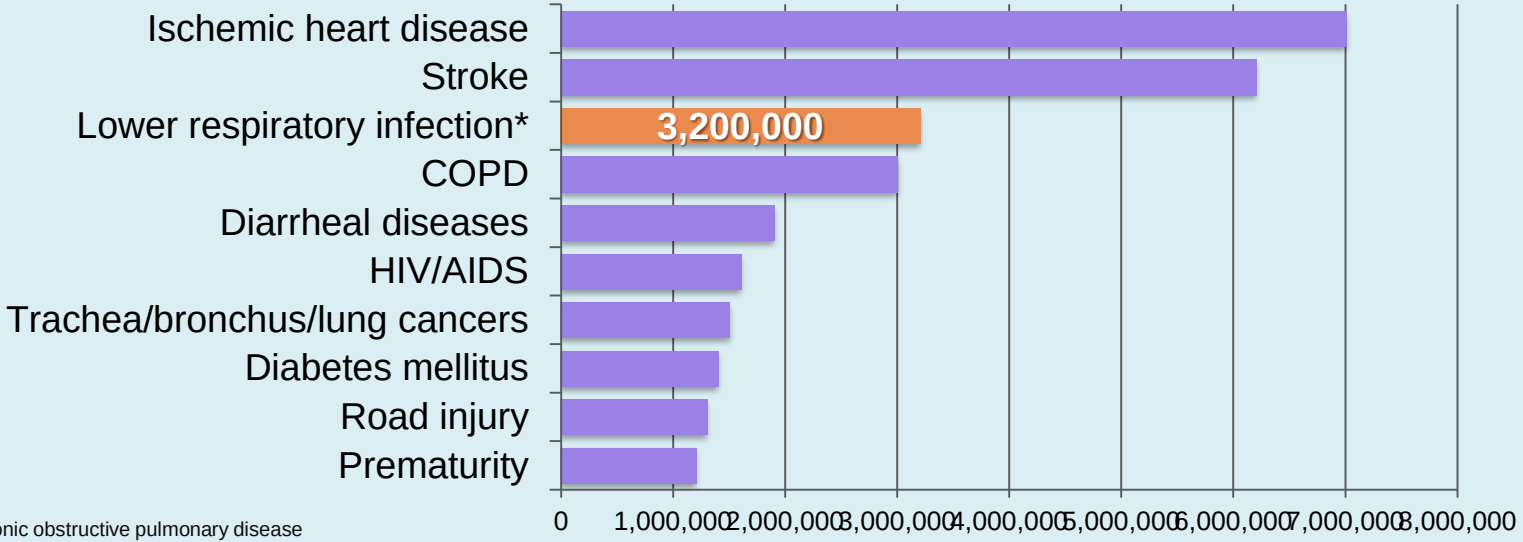
Learning Objectives

- Describe the results of clinical trials of new vaccines against (influenza), pneumococcus and herpes zoster
- Explore how the benefits of vaccination extend beyond the individual and the target population, and may contribute to prevention of antimicrobial resistance

Lower respiratory tract infections, including pneumonia: 3rd leading cause of death worldwide

The 10 Leading Causes of Death in the World, 2011[1]

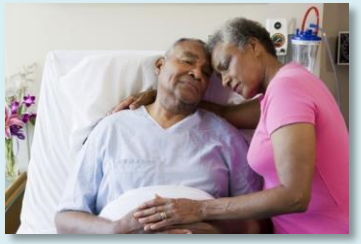


COPD = chronic obstructive pulmonary disease

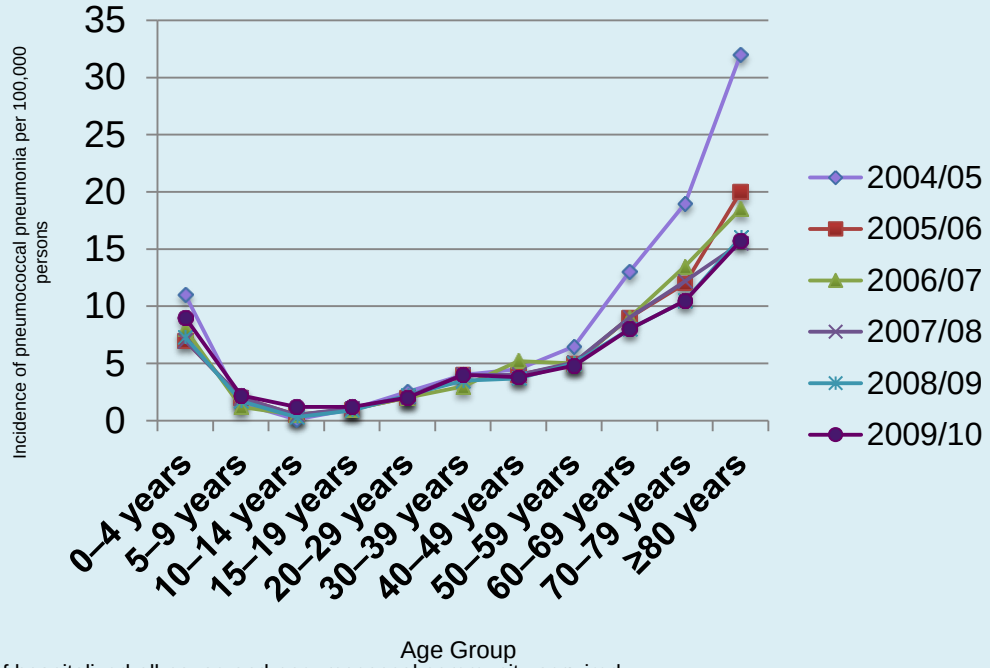
* Pneumococcal pneumonia is the leading known cause of lower respiratory tract infection mortality.[2]

1. WHO. Media Centre Fact Sheets. http://www.who.int/mediacentre/factsheets/fs310/en/index.html. Updated July 2013. Accessed December 18, 2013.
2. Lozano R et al. *Lancet*. 2012;380(9859):2095-2128.

Hospitalization due to pneumococcal pneumonia increases with age



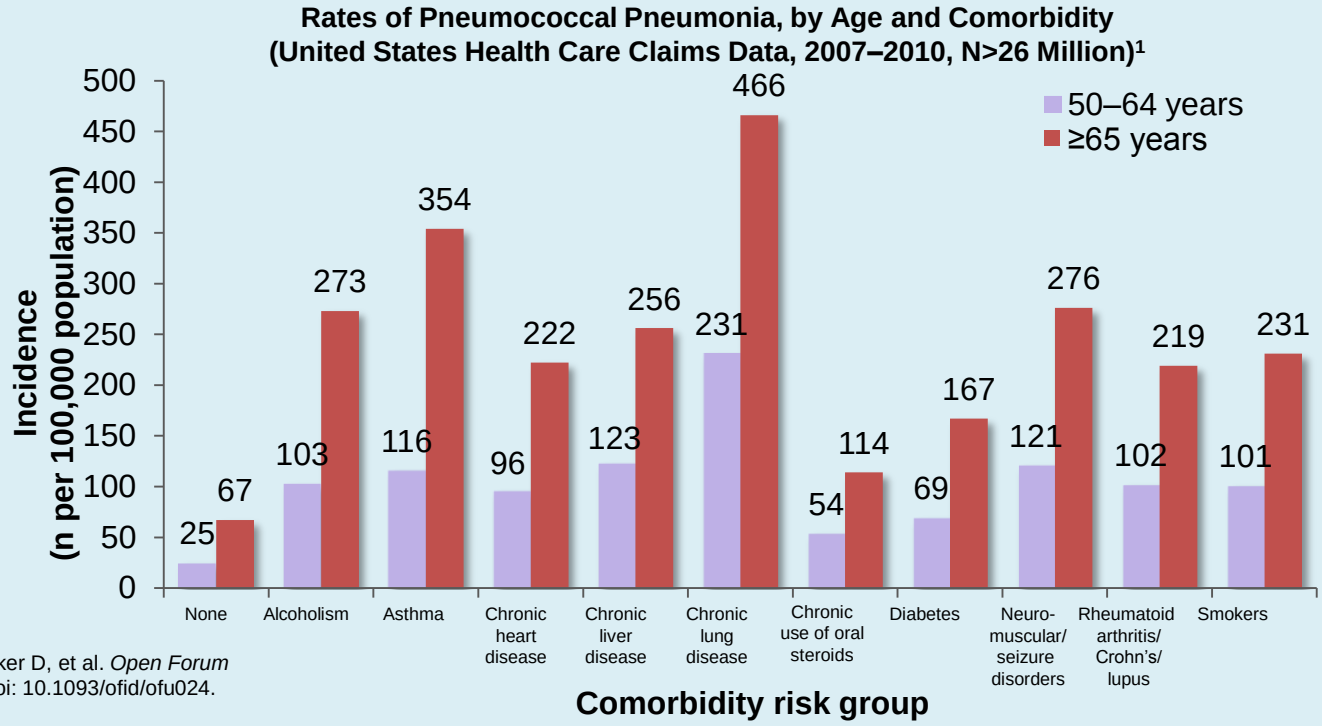
CIHI DAD annual incidence of hospitalizations in Canada 2004/05 to 2009/10 due to pneumococcal pneumonia by age and year



CIHI = Canadian Institute for Health Information
DAD = Discharge Abstract Database

SA McNeil et al. A retrospective study of the clinical burden of hospitalized all-cause and pneumococcal community acquired pneumonia in Canada. Can Resp J 2015.

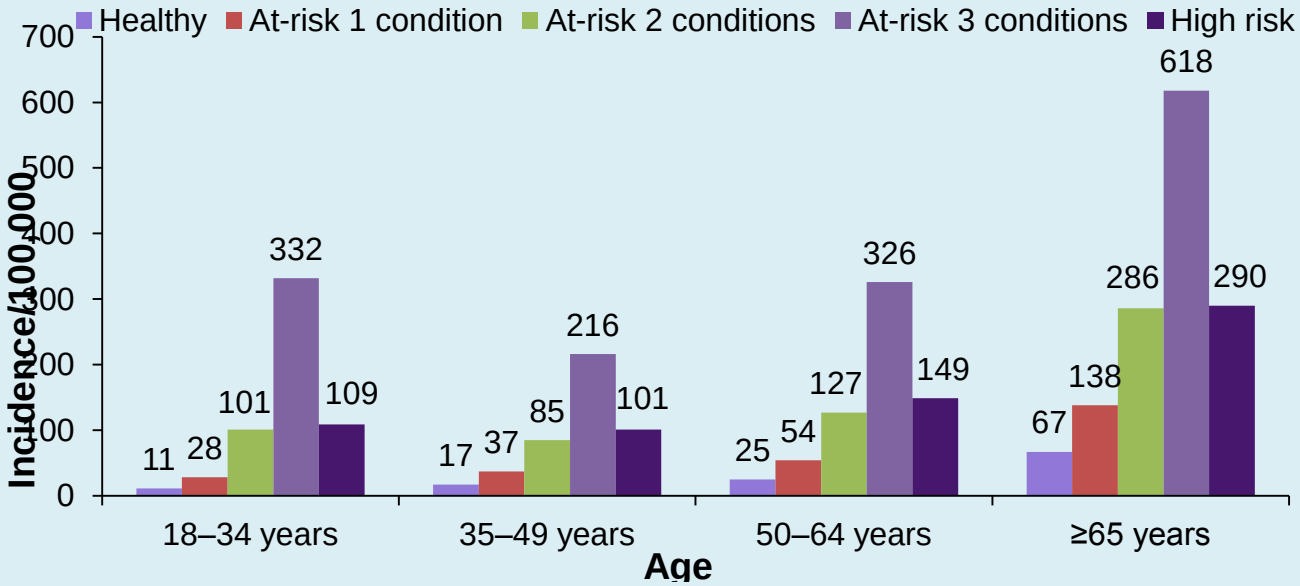
Comorbidities increase pneumococcal pneumonia risk in adults



Shea KM, Edelsberg J, Weycker D, et al. *Open Forum Infect Dis* 2014;1(1):ofu024. doi: 10.1093/ofid/ofu024.

Multiple underlying medical conditions further increase pneumococcal pneumonia risk in adults

Estimated annual incidence of pneumococcal pneumonia in the United States in adults, by number of comorbidities



Note: At-risk—immunocompetent with ≥1 selected chronic condition, including alcoholism, asthma, chronic heart disease, chronic liver disease, chronic lung disease, diabetes, neuromuscular/seizure disorders, and smoking.

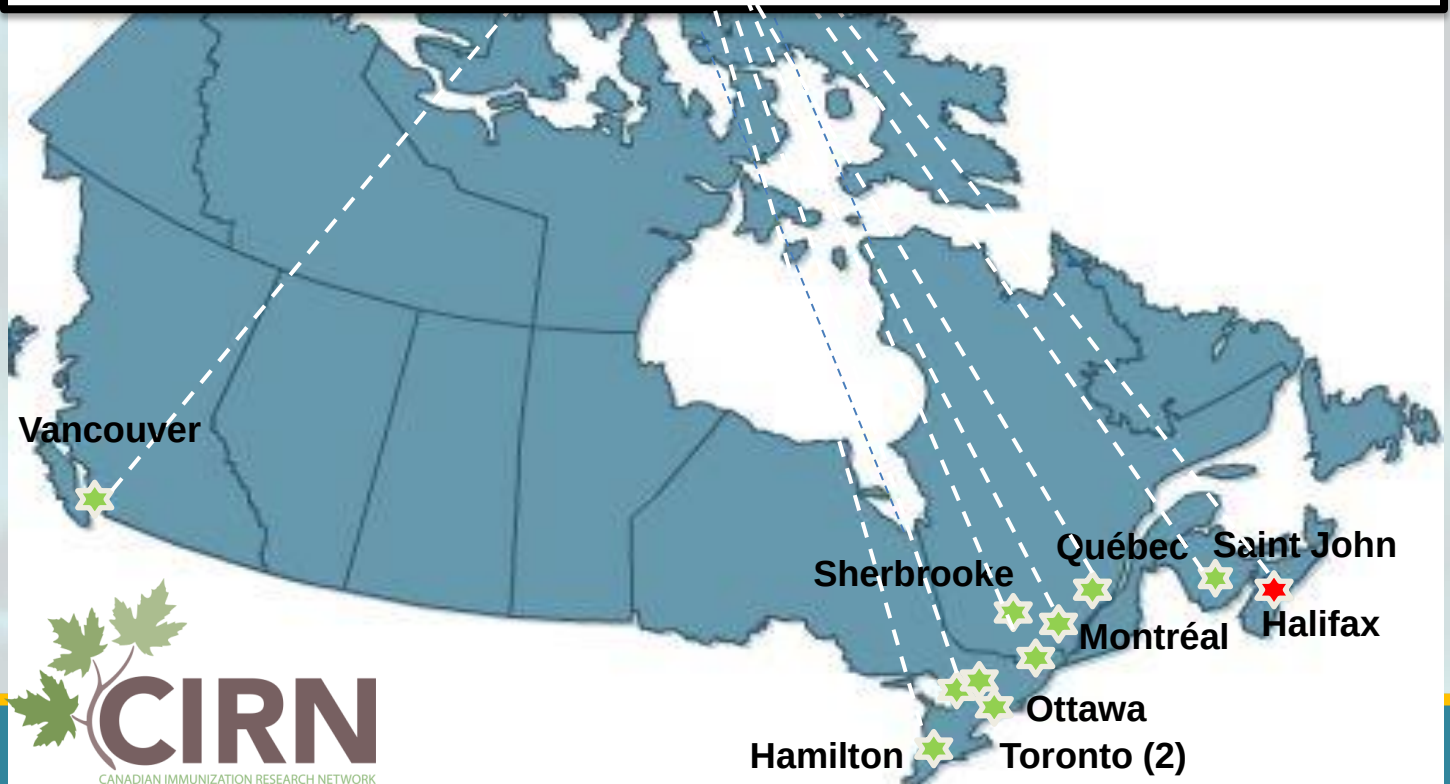
1. Shea KM, et al. *Open Forum Infect Dis. 2014 May 27;1(1)*. doi:10.1093/ofid/ofu024. **2.** Data on file. Pfizer Inc, New York, NY.

Canadian Immunization Research Network (CIRN) Serious Outcomes Surveillance (SOS) Network

- CAP/IPD surveillance started in 2011; Comprised of 9 adults hospitals in 5 provinces

[1]*LeBlanc J….McNeil SA, et al. Vaccine 2017 Jun 22;35(29):3647-54*

[2]*LeBlanc J,…McNeil SA, et al. ISPPD-11, April 15-19, 2018 (Poster #396/SP03)*



S. pneumoniae is the leading cause of hospitalized CAP in Canada

Variable	Proportion (%) by year(s)						
	2011	2012	2013	2014	2015	2010-2013	2014-2015
Spn pos/CAP tested	**22.1** (25/113)	**26.3** (46/175)	**22.0** (72/328)	**10.2** (36/353)	**14.3** (32/224)	**23.2** (144/621)	**11.8** (68/577)
PCV7	0.9 (1/113)	0.0 (0/175)	0.8 (2/328)	0.6 (2/353)	0.9 (2/224)	0.5 (3/621)	0.7 (4/577)
PCV13	**17.7** (20/113)	**17.1** (30/175)	**12.8** (42/328)	**6.2** (22/353)	**8.5** (19/224)	**14.8** (92/621)	**7.1** (41/577)
PPV23 (non-PCV13)	0.9 (1/113)	1.7 (3/175)	2.4 (8/328)	0.8 (3/353)	1.8 (4/224)	1.9 (12/621)	1.2 (7/577)
NVT	0.9 (1/113)	2.3 (4/175)	2.1 (7/328)	1.4 (5/353)	1.3 (3/224)	1.9 (12/621)	1.4 (8/577)

[1]*LeBlanc J….McNeil SA, et al. Vaccine 2017 Jun 22;35(29):3647-54*
[2]*LeBlanc J,…McNeil SA, et al. ISPPD-11, April 15-19, 2018 (Poster #396/SP03)*

Clinical characteristics of adults hospitalized with CAP, Canada (2010-2015) n=6687

	S. pneumo-negative			S. pneumo-positive	
	2010-2013[3] (n=3302)	2014-2015 (n=2550)		2010-2013[3] (n=549)	2014-2015 (n=286)
Age; mean +/- SD (range)	68.5 +/- 16.7 (17-104)	68.8 +/- 16.6 (18-108)		62.4 +/- 17.1 (20-100)	62.2 +/- 16.1 (19-103)
Gender (male); %	53.7 (1772/3302)	54.3 (1385/2550)		53.9 (296/549)	50.4 (144/286)
≥ 1 co-morbidity; %	93.8 (3098/3302)	94.0 (2397/2550)		88.2 (484/549)	86.7 (248/286)
Immunocompromised; %	31.2 (1030/3302)	24.8 (631/2550)		27.9 (153/549)	23.4 (67/296)
Current/past smoker; %	68.0 (2096/3081)	69.7 (1628/2337)		70.6 (370/524)	72.5 (190/262)
Obesity (body mass index ≥30); %	25.8 (734/2841)	29.3 (641/1909)		21.3 (102/479)	25.5 (63/247)
Concomitant influenza infection; %	13.9 (220/1588)	21.9 (461/2109)		15.6 (43/276)	20.2 (48/238)
Pneumococcal vaccine; %	53.7 (1200/2235)	76.0 (1536/2021)		40.4 (163/403)	64.9 (148/228)

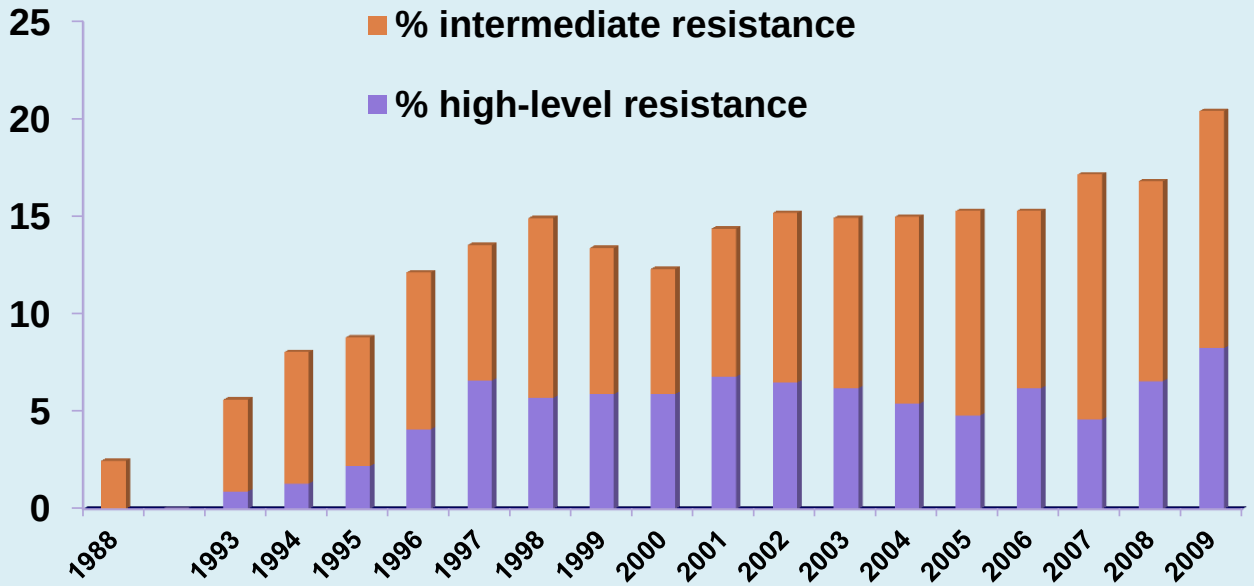
[1]*LeBlanc J….McNeil SA, et al. Vaccine 2017 Jun 22;35(29):3647-54*
[2]*LeBlanc J,…McNeil SA, et al. ISPPD-11, April 15-19, 2018 (Poster #396/SP03)*

Hospitalized CAP is associated with significant morbidity and mortality

	S. pneumo-negative		S. pneumo-positive	
	2010-2013[1] (n=3302)	2014-2015[2] (n=2550)	2010-2013[1] (n=549)	2014-2015[2] (n=286)
30-day mortality; %	11.4 (375/3302)	11.5 (292/2550)	9.7 (53/549)	5.9 (17/286)
LOS in days; Mean (range; Q75)	11.8 (1-384; 14)	10.8 (1-136; 13)	12.5 (1-105; 14)	9.9 (1-126; 11)
ICU admission; %	17.7 (584/3302)	18.3 (467/2550)	29.3 (161/549)	30.4 (87/286)
Mechanical ventilation; %	11.7 (386/3302)	11.3 (289/2550)	20.2 (111/549)	20.3 (58/286)
Any complication; %	53.6 (1769/3299)	54.1 (1376/2550)	57.1 (313/548)	53.5 (153/286)
New arrhythmia; %	10.5 (185/1769)	7.6 (104/1376)	13.4[3] (42/313)	7.8 (12/153)
Congestive heart failure; %	9.0 (90/998)	6.5 (90/1376)	5.5 (9/165)	4.6 (7/153)
Myocardial infarction; %	4.2 (74/1769)	4.4 (60/1376)	2.6 (8/313)	2.6 (4/153)
Unstable angina; %	0.7 (13/1769)	0.1 (1/1376)	0.0 (0/313)	0.0 (0/153)

Antimicrobial resistance: Percentage of penicillin non-susceptible *S. pneumoniae* in Canada (1988–2009)

Mean 2012-1016 Penicillin non-susceptible rate = **10.4%**



Non-meningitis, Oral pen breakpoints used

Canadian Bacterial Surveillance Network, Jun 2010. Available at: http://microbiology.mtsinai.on.ca/data/sp/sp_2009.shtml#figure1

Serotype 19A is multi-drug resistant

Susceptibility (%S), BESST (2007-2009) vs. SAVE (2011/12)

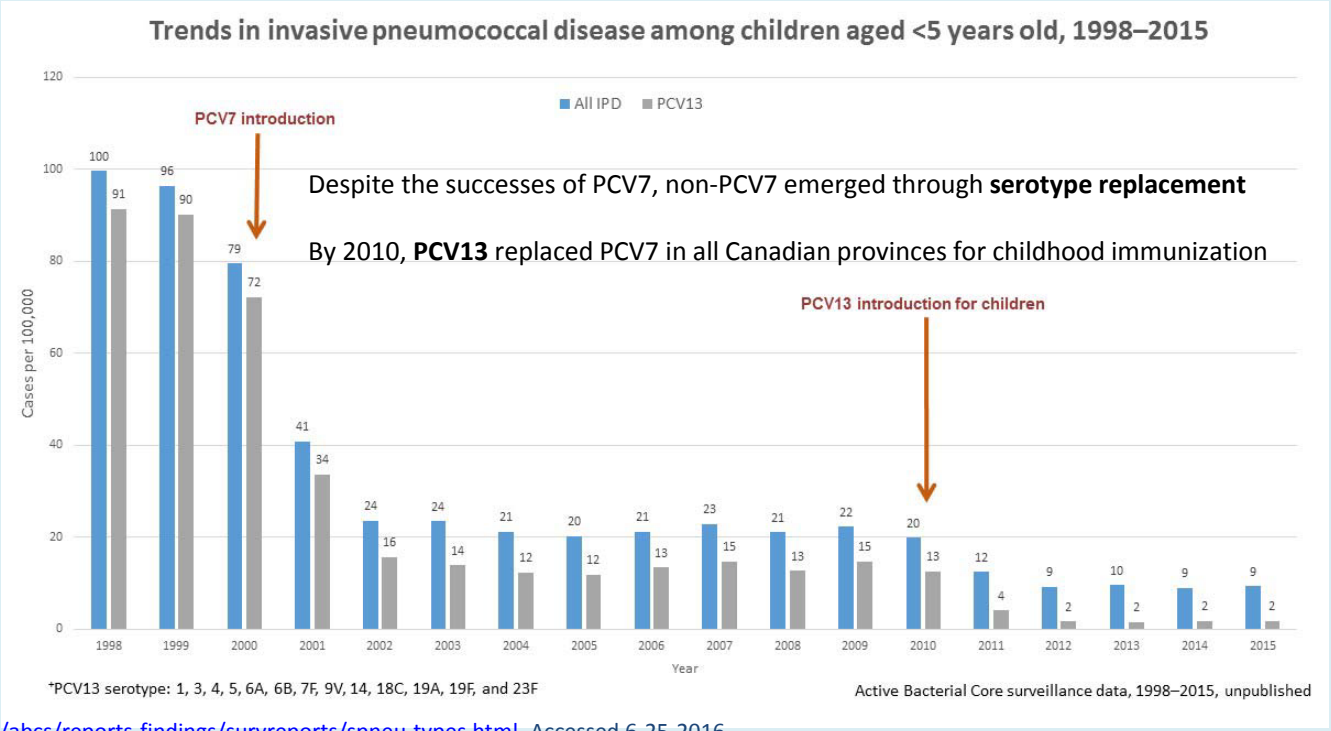
ST	PEN (iv, M)	PEN (iv, NM)	CRO (M)	CRO (NM)	CLR	LVX	SXT	DOX	%MDR
7F	100/99	100/100	100/100	100/100	100/97	100/100	100/100	100/98	0/1
19A	54/62	98/82	98/78	100/91	73/40	100/99	78/68	85/70	14/26
22F	96/99	100/100	100/100	100/100	96/78	100/99	100/100	100/99	0/1
3	100/100	100/100	100/100	100/100	95/95	100/100	100/98	100/93	0/2
12F	100/100	100/100	100/100	100/100	45/32	100/100	100/97	100/99	0/0
15A	67/33	100/100	100/93	100/100	42/19	100/100	100/93	42/22	33/69
6C	100/82	100/100	100/98	100/100	75/80	100/100	100/87	100/93	0/6
11A	100/100	100/100	100/100	100/100	92/71	100/100	100/78	100/100	0/0
9N	100/100	100/100	100/100	100/100	100/93	100/100	100/96	100/97	0/0
23A	63/71	100/100	100/100	100/100	100/87	100/99	91/93	100/84	0/3

ST = serotype; M = meningitis; NM = nonmeningitis; PEN = penicillin; CRO = ceftriaxone; CLR = clarithromycin; LVX = levofloxacin; SXT = trimethoprim-sulfamethoxazole; DOX = doxycycline; MDR = multi-drug resistance

Adam et al. ICAAC 2013

CANADIAN ANTIMICROBIAL RESISTANCE ALLIANCE CARA

Rates of IPD in Children <5y in US (1998-2015)

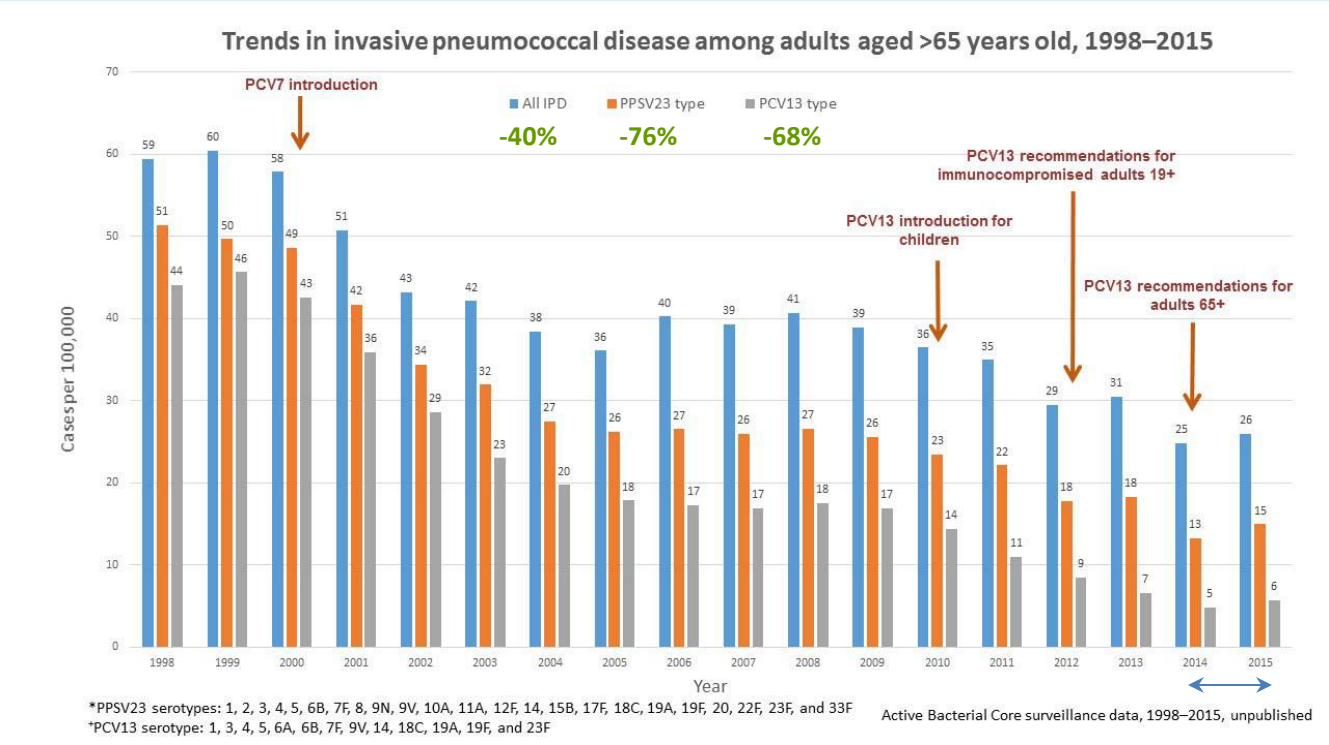


Source: http://www.cdc.gov/abcs/reports-findings/survreports/spneu-types.html Accessed 6-25-2016

Rates of IPD in adults 65+ in US (1998-2015)

CDC Active Bacterial Core Surveillance, USA Presented by Matanock A. ACIP Oct. 26, 2017

Protection observed in unvaccinated children and adults through **herd immunity**



Vaccine- preventable CAP among hospitalized adults in Canada

Variable	Proportion (%) by year(s)						
	2011	2012	2013	2014	2015	2010-2013	2014-2015
Spn pos/CAP tested	**22.1** (25/113)	**26.3** (46/175)	**22.0** (72/328)	**10.2** (36/353)	**14.3** (32/224)	**23.2** (144/621)	**11.8** (68/577)
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PCV13	**17.7** (20/113)	**17.1** (30/175)	**12.8** (42/328)	**6.2** (22/353)	**8.5** (19/224)	**14.8** (92/621)	**7.1** (41/577)
PPV23 (non-PCV13)	0.9 (1/113)	1.7 (3/175)	2.4 (8/328)	0.8 (3/353)	1.8 (4/224)	1.9 (12/621)	1.2 (7/577)
NVT	0.9 (1/113)	2.3 (4/175)	2.1 (7/328)	1.4 (5/353)	1.3 (3/224)	1.9 (12/621)	1.4 (8/577)

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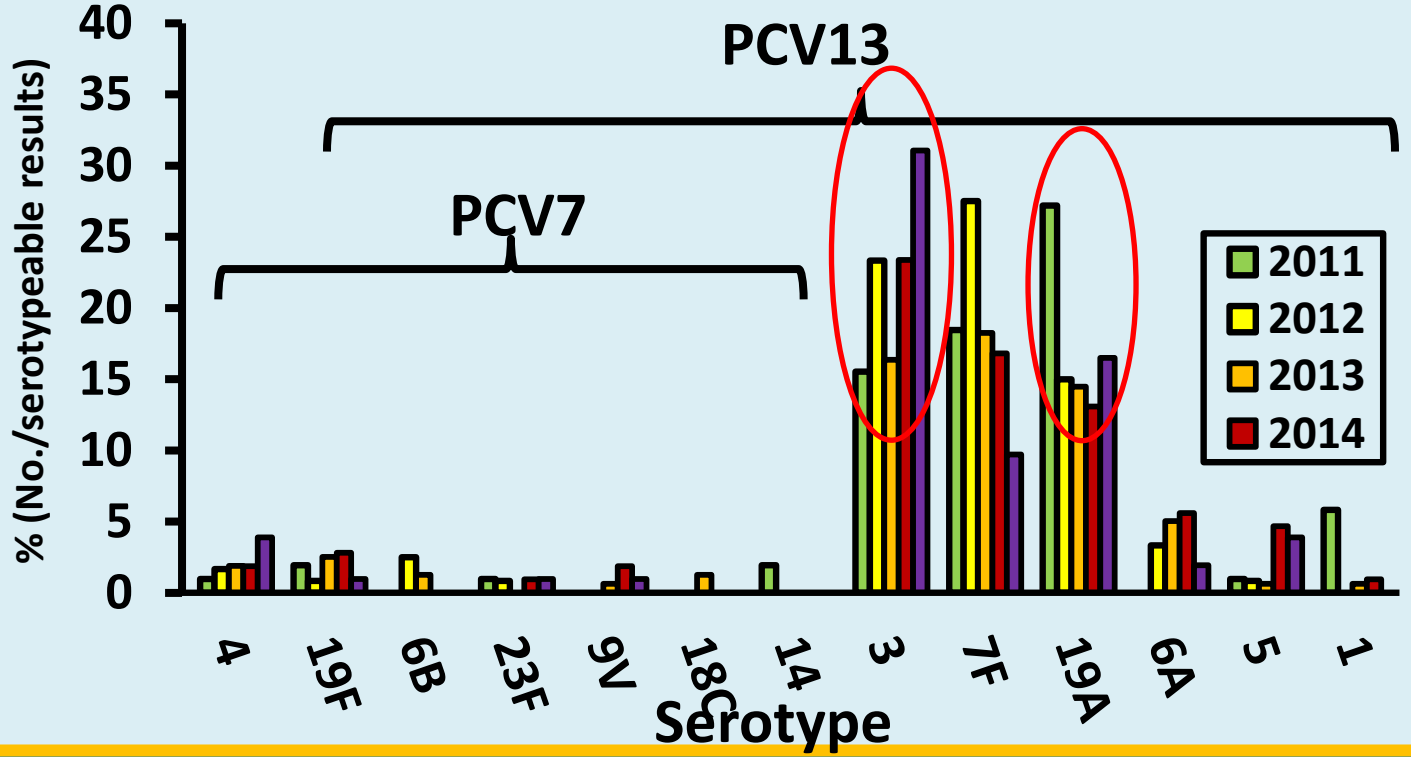
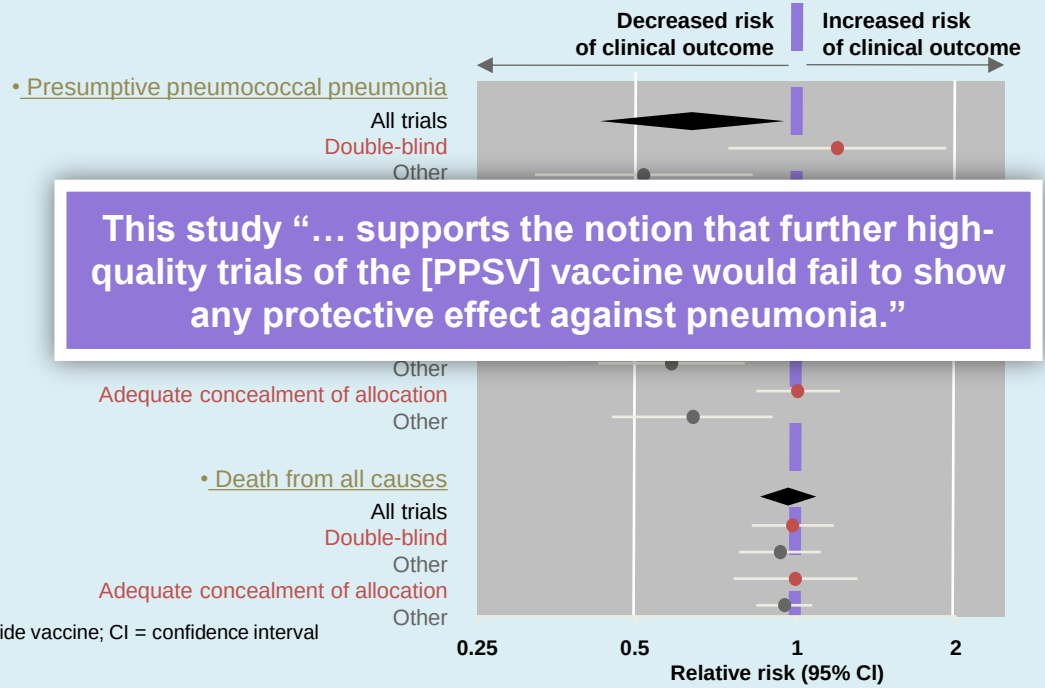
[2]*LeBlanc J,…McNeil SA, et al. ISPPD-11, April 15-19, 2018 (Poster #396/SP03)*

S. pneumoniae serotype distribution in hospitalized CAP in adults (Canada; 2011-2015)



Efficacy of pneumococcal polysaccharide vaccination in adults: a meta-analysis

Summary plot of meta-analysis of 22 PPSV trials from 101,507 individuals



This study "… supports the notion that further high-quality trials of the [PPSV] vaccine would fail to show any protective effect against pneumonia."

PPSV = pneumococcal polysaccharide vaccine; CI = confidence interval

Huss A, et al. *CMAJ.* 2009;180:48-58.

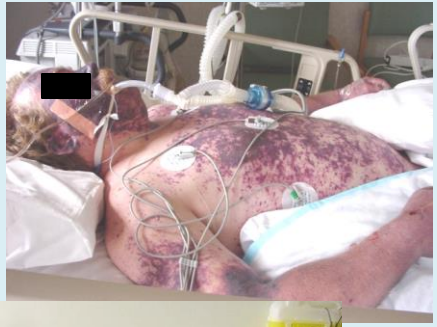
Is PCV13 better than PPV23 in adults? Immunogenicity

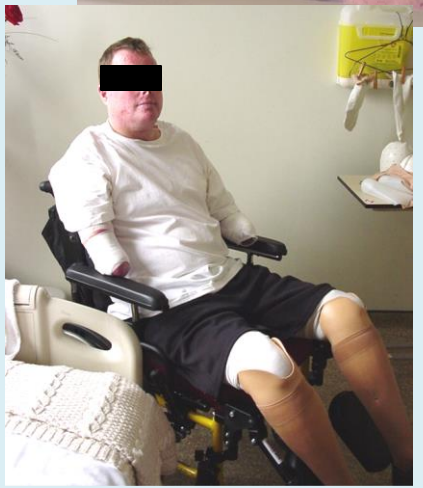
- Mixed results when immunogenicity of PCV-7 compared to PPV-23:
  - Liver transplant: Not more immunogenic *Kumar CID 2008;47(7)*
  - Renal transplant: Better response to 2/7 serotypes but no difference at 3y *Kumar JID 2003;187(10)*
  - HSCT: Better response at 12mos (90.8% vs 55.6%; p=0.02) *Kumar CID 2007;45(12)*
  - Elderly: Better early response but no diff by 1y

Jackson Vaccine 2007;25(20)

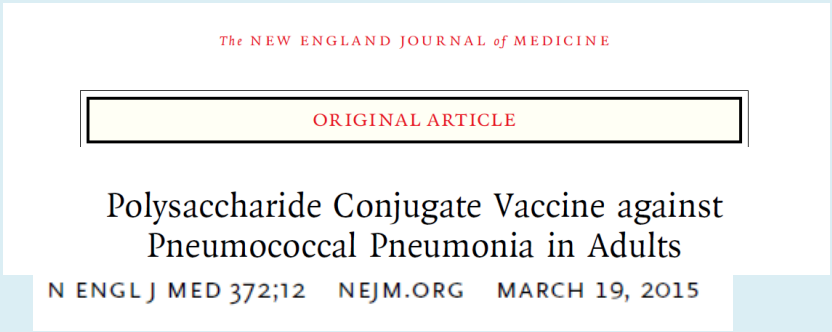
Cochrane: Conclusions

- Results of meta-analysis supports the use of PPV to prevent IPD
- Minimal benefit for all-cause pneumonia
- Does not support the routine use of PPV to prevent all-cause pneumonia or mortality





Huss A, et al. *CMAJ.* 2009;180:48-58.



CAPiTA

- Randomized, double-blind, placebo-controlled trial (Sept. 2008- Aug. 2013)
- N= ~42,000 per arm
- CAP confirmed by CXR and etiology assessed using novel type-specific urinary antigen
- Mean duration of follow-up = 4y

CAPiTA- Results

- First episode vaccine-type CAP- 49 cases vs 90 cases: VE 45.6% (95%CI: 21.8-62.5%)
  - **NNV= 1110 (760-3500)**
- First episode vaccine-type non-invasive, non-bacteremic CAP- 33 vs 60: VE 45.0% (95%CI: 14.2-65.3%)
  - **NNV= 1620 (1110-5130)**
- First episode vaccine-type IPD- 7 vs 28: VE 75.0% (41.4-90.8%)
  - **NNV= 2128**
- All-cause CAP – 747 vs 787: VE 5.1% (-5.1-14.2%)

Policy considerations for use of PCV13 in older adults

- Burden/incidence of pneumococcal disease in adults- IPD and CAP
- Serotype distribution of *S. pneumoniae* causing CAP in adults given routine PCV13 use in infants since 2011 (residual disease burden)
- Feasibility/acceptability of use of 2 pneumococcal vaccines in older adults
- Cost effectiveness/budget impact

NACI Pneumococcal vaccine recommendations: Immunocompetent Adults

- Indications: Age ≥65y, underlying comorbidities (including asthma), smoking, illicit drug use, homeless
- Single dose of PPSV23
- If PPSV23 dose given before age 65y, give **one** additional dose ≥ 65; interval= 5y
- PCV13: Good evidence to recommend PCV13 followed by PPV23 in immunocompetent adults 65+ not previously immunized against pneumococcal disease for prevention of CAP and IPD (NACI)

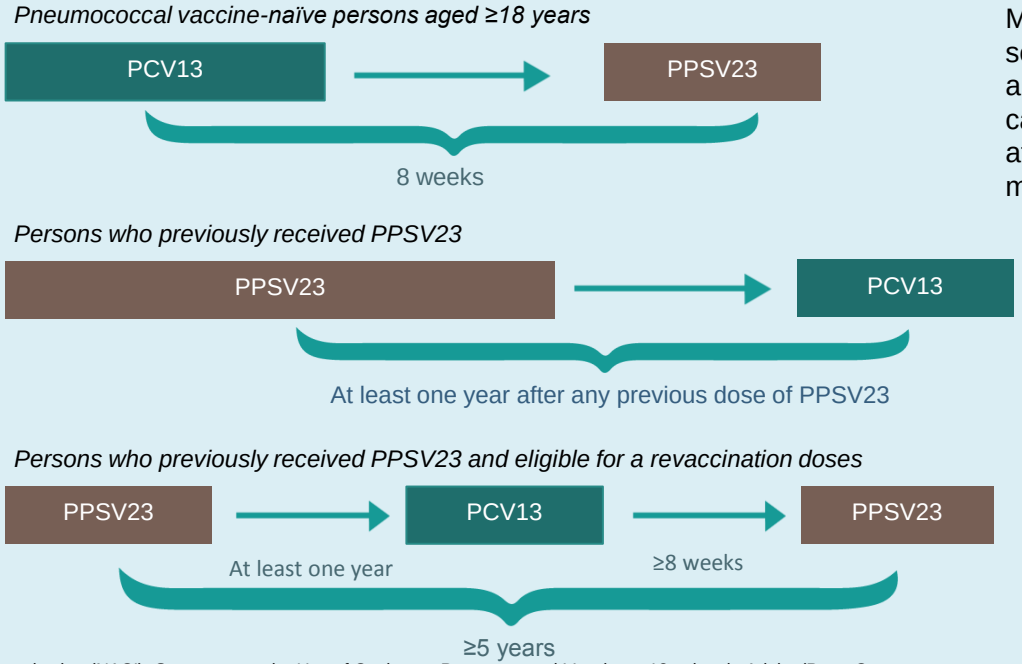
http://publications.gc.ca/collections/collection_2015/aspc-phac/HP40-135-2015-eng.pdf

Immunocompromised Adults

- Functional or anatomical asplenia (remember IBD)
- Sickle cell disease
- Hepatic cirrhosis
- Chronic renal failure or nephrotic syndrome
- HIV
- Other immunocompromising conditions/meds

- **PCV13** X 1 lifetime dose
- PLUS **TWO** doses **PPSV 23** (5y apart); one additional dose at age 65y if both doses provided <65y

Pneumococcal conjugate vaccine (PCV13) dose sequence — NACI recommendations



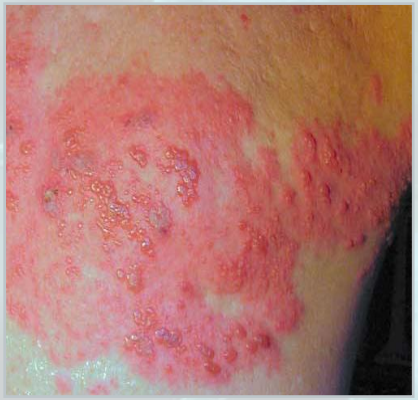
Minimum interval between sequential administration of PCV13 and PPSV23 is 8 weeks; PPSV23 can be given later than 8 weeks after PCV13 if this window is missed.

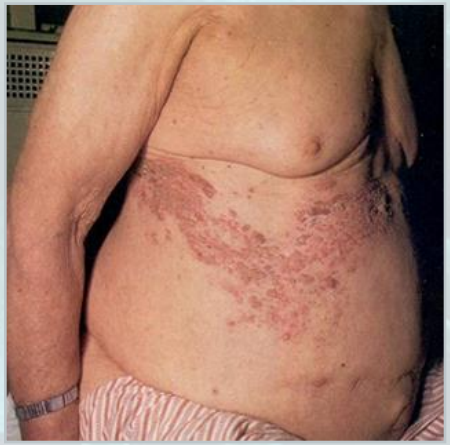
PHAC. National Advisory Committee on Immunization (NACI). Statement on the Use of Conjugate Pneumococcal Vaccine – 13 valent in Adults (Pneu-C-13). Available at: http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/13vol39/acs-dcc-5/index-eng.php

Take home messages

- Pneumococcal disease causes significant morbidity and mortality in older adults and is a major driver of antimicrobial use
- Pneumococcal vaccination of both children and adults reduces hospitalization and complications in adults
- Pneumococcal vaccination has led to reduced AMR in *S. pneumoniae* due to shift in serotype prevalence without associated increase in morbidity
- All older adults should receive PPSV23 and should be offered PCV13

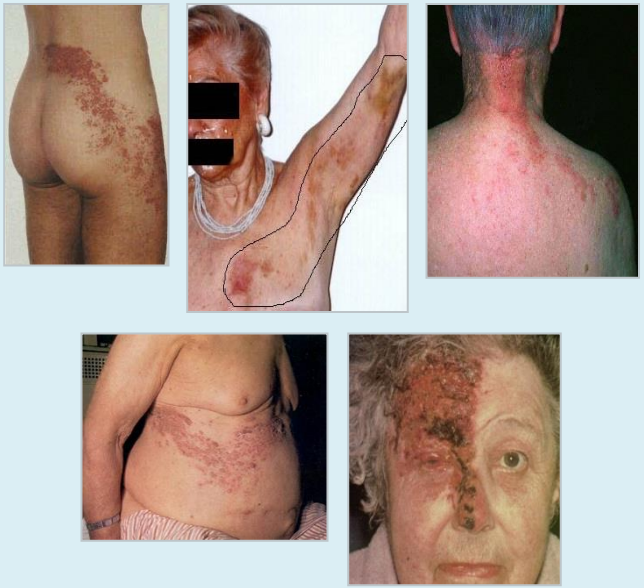
Improved Vaccine for the Prevention of Shingles

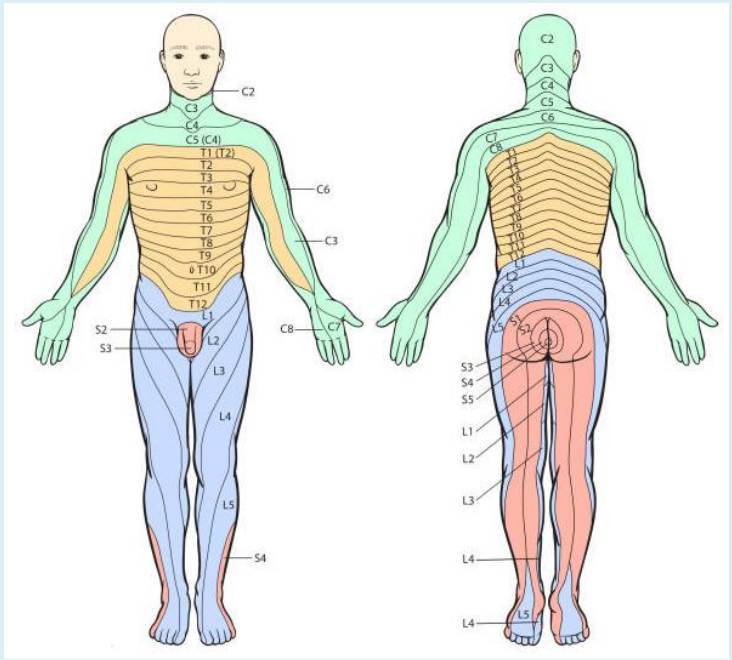




Shingles

- Shingles is a painful vesicular eruption in a dermatomal distribution





Dermatomes are areas on the skin supplied by sensory fibers of the spinal nerves

HZ Burden and Complications

- 1 out of 3 Canadians will experience an episode of HZ in their lifetime
  - 1 out of 2 for those aged 85 years and older
- Complications can severely affect the patient's quality of life

ACUTE
HZ PAIN
- **loss of work**
- **low quality of life**

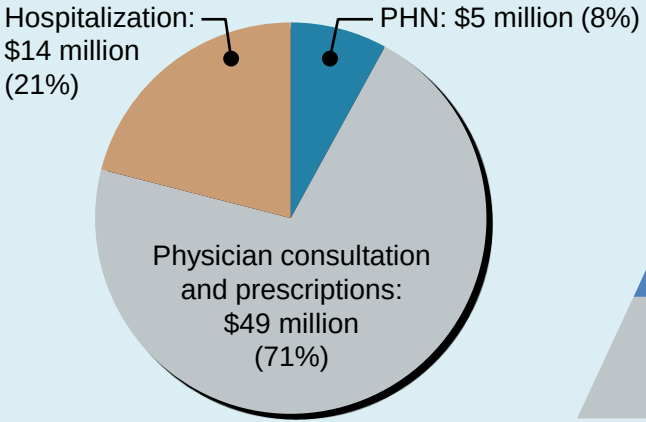
PHN (10-22%)
Ocular complications
Scarring
Secondary bacterial infections

Stroke

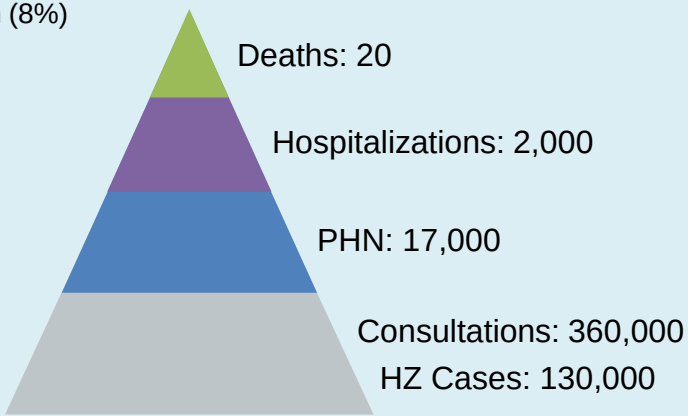
Estimated Annual Burden of HZ in Canada

HZ = herpes zoster; PHN = postherpetic neuralgia; QALY = quality-adjusted life year.
Brisson M, et al. Hum Vaccin 2008; 4(3):238-45.

2005 Healthcare Cost: $69 Million



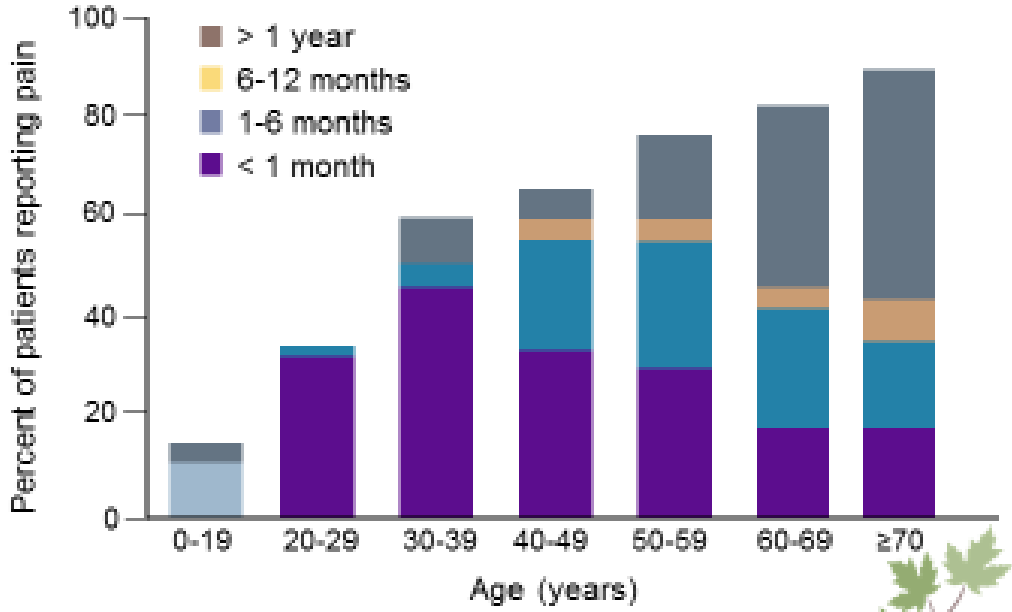
Number of HZ-related Events in Canada



Conclusion:
Vaccinating 65-year-old adults yields a $33,000 cost per QALY gained (usual threshold is $50,000)

Prevalence and Duration of PHN (PHN: Pain for > 30 Days After Rash Onset)

Prevalence and duration of acute pain and PHN increase with age



de Moragas JM, et al. AMA Arch Derm 1957; 75(2):193-6.
Kost RG, et al. N Engl J Med 1996; 335(1):32-42.

CIRN
IRN
JNIZATION RESEARCH NETWORK

Live-attenuated VZV vaccine: Summary of post-marketing Effectiveness

Table 1 Summary of the characteristics and results from three retrospective cohort (nested case–control) studies assessing the effectiveness of the live-attenuated herpes zoster vaccine, Zostavax, in immunocompetent subjects

Characteristics					Vaccine effectiveness, % (95% CI)			
Study ID	Study setting/ period	Median follow-up, years	Population	Total/vaccinated subjects	Herpes zoster	Post-herpetic neuralgia	Ophthalmic zoster	Hospitalization for herpes zoster
Tseng et al. [35]	KPSC/ 2007–2009	1.6	Immunocompetent subjects aged ≥60 years	303,044/75,761	55 (52; 58)	NA	63 (39; 77)	65 (49; 76)
Langan et al. [36]	Medicare/ 2007–2009	1.6	Immunocompetent and immunocompromised subjects aged ≥65 years	766,330/29,785[a] 625,409/24,392[b]	48 (39; 56)[a] 51 (41; 59)[b]	62 (37; 77)[c] 59 (21; 79)[d]	NA	NA
Tseng et al. [37]	KPSC/ 2007–2014	Not reported	Immunocompetent subjects aged ≥60 years	704,312/176,078	51 (50; 53)	NA	NA	NA

KPSC Kaiser Permanente Southern California, *CI* confidence interval, *NA* not assessed

[a] Overall study population (immunocompetent and immunocompromised subjects)

[b] Only immunocompetent subjects

[c] Postherpetic neuralgia at 30 days

[d] Postherpetic neuralgia at 90 days

Ansaldi et al., Adv Ther (2016) 33:1094–1104

Vaccine effectiveness in immunocompromised adults

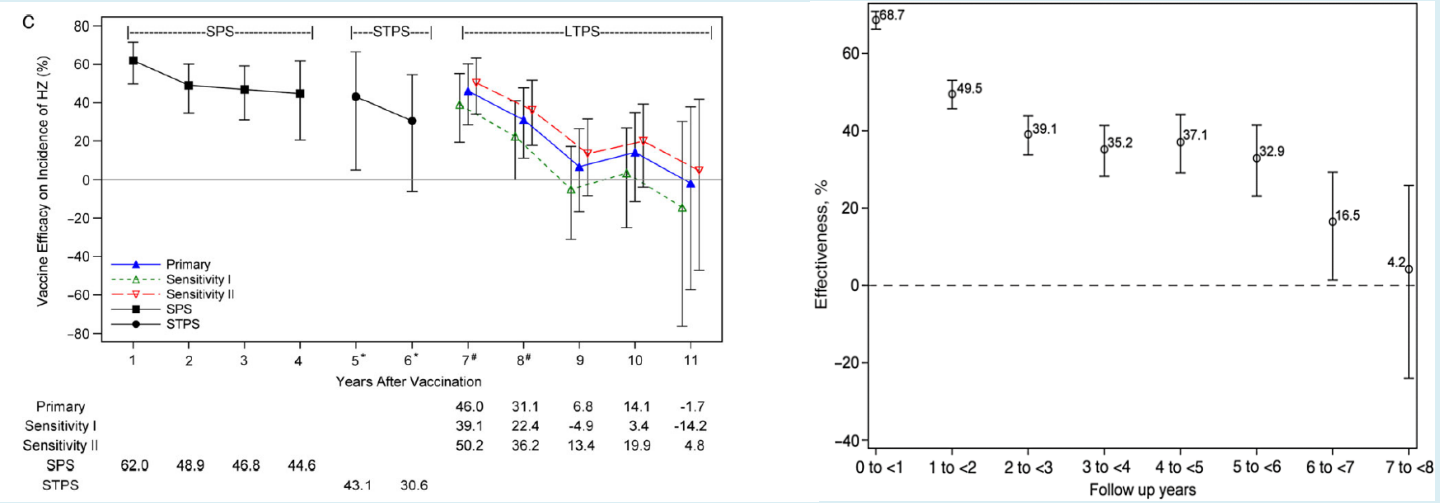
Characteristics						Results		
Study ID	Study setting/ period	Median follow-up, days	Population	Total/vaccinated subjects	VCR, %	HZ incidence per 1000 person-years (95% CI)		VE against HZ, % (95% CI)
						Vaccinated	Unvaccinated	
Zhang et al. [49]	Medicare/ 2006–2009	730	Individuals diagnosed with rheumatoid arthritis, psoriatic arthritis, psoriasis, ankylosing spondylitis or inflammatory bowel disease (Crohn's disease or ulcerative colitis) aged ≥60 years	463,541/18,683	4.0	6.7 (5.7; 7.9)	11.6 (11.4; 11.9)	49 (29;48)
Langan et al. [36]	Medicare/ 2007–2009	584	Individuals with rheumatoid arthritis, inflammatory bowel disease aged ≥65 years (34% aged ≥80 years)	140,925/5531	2.3	5.4 (4.6; 6.4)	10.0 (9.8; 10.2)	37 (6; 58)[b]
Tseng et al. [50]	KPSC/ 2007–2012	730	Individuals who had received chemotherapy with myelosuppressive agents aged ≥60 years	21,476/4710	21.9	12.9 (10.5; 15.8)	22.1 (20.3; 23.9)	42 (27; 54)[a]

KPSC Kaiser Permanente Southern California, *CI* confidence interval, *VCR* vaccine coverage rate, *VE* vaccine effectiveness
[a] Adjusted VE against HZ
[b] VE in immunosuppressed individuals

KPSC Kaiser Permanente Southern California, CI confidence interval, VCR vaccine coverage rate, VE vaccine effectiveness
a Adjusted VE against HZ
b VE in immunosuppressed individuals

Ansaldi et al., Adv Ther (2016) 33:1094–1104

Live attenuated VZV Vaccine Duration of Protection



Morrison VA, et al. Clin Infect Dis 2014; [epub ahead of print].

J Infect Dis. 2016;213(12):1872-1875. doi:10.1093/infdis/jiw047

Duration of protection against PHN

Table 5. Effectiveness of ZOSTAVAX in reducing the risk of PHN by age at vaccination and time since vaccination

	Age at Vaccination								All Ages Combined
	50-59 Years		60-69 Years		70-79 Years		80+ Years		
	PHN Cases	VE % (95% CI)	PHN Cases	VE % (95% CI)	PHN Cases	VE % (95% CI)	PHN Cases	VE % (95% CI)	VE % (95% CI)
Overall VE	5	63% (11, 85)	119	71% (65, 76)	134	70% (63, 75)	64	62% (50, 71)	**69% (65, 72)**
Time since vaccination (years)									
30 days to <1 year	4	31% (-85, 75)	15	85% (75, 91)	15	86% (76, 92)	13	77% (61, 87)	82% (76, 87)
1 to <2 years	1	81% (-39, 97)	27	67% (51, 77)	30	66% (50, 76)	13	65% (40, 80)	66% (57, 73)
2 to <3 years	0		21	67% (49, 79)	28	60% (42, 73)	15	38% (-3, 63)	60% (49, 69)
3 to <4 years	0		16	71% (53, 83)	17	70% (52, 82)	8	53% (5, 77)	68% (57, 77)
4 to <5 years			17	64% (41, 78)	22	55% (31, 71)	5	62% (9, 85)	60% (45, 70)
5 to <6 years			14	61% (33, 77)	12	69% (44, 82)	6	34% (-49, 71)	61% (45, 73)
6 to <7 years			5	78% (47, 91)	9	62% (26, 81)	4	22% (-114,71)	65% (44, 79)
7 to <8 years			4	47% (-44, 81)	1	87% (8, 98)	0	~	70% (28, 88)

VE was calculated as (1-hazard ratio)*100.
Cox models adjusted for calendar time, age, sex, race/ethnic group, healthcare resource utilization (flu vaccination, # of weeks of outpatient visits per year), comorbid conditions (DxCG score, HCUP risk score), immunocompromised status during follow-up.
Abbreviations: VE denotes vaccine effectiveness; CI confidence interval; DxCG diagnostic cost group; HCUP healthcare cost and utilization project.

Marks M, Barlett J, Fireman B et al. Poster presented at: Canadian Pain Society Annual Scientific Meeting 2017 May 23-26; Halifax CA

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Efficacy of an Adjuvanted Herpes Zoster Subunit Vaccine in Older Adults

Himal Lal, M.D., Anthony L. Cunningham, M.B., B.S., M.D., Olivier Godeaux, M.D., Roman Chlibek, M.D., Ph.D., Javier Diez-Domingo, M.D., Ph.D., Shinn-Jang Hwang, M.D., Myron J. Levin, M.D., Janet E. McElhaney, M.D., Airi Poder, M.D., Joan Puig-Barberà, M.D., M.P.H., Ph.D., Timo Vesikari, M.D., Ph.D., Daisuke Watanabe, M.D., Ph.D., Lily Weckx, M.D., Ph.D., Toufik Zahaf, Ph.D., and Thomas C. Heineman, M.D., Ph.D., for the ZOE-50 Study Group*

Recombinant adjuvanted subunit vaccine

- Glycoprotein E
- $ASO1_B$- MPL + QS21 – novel adjuvant which stimulates strong CD4 T cells and humoral responses
- RDBPC trial- n= ~7700/arm, healthy adults 50+y
- Vaccine vs placebo IM at 0, 2 mos

Vaccine Efficacy

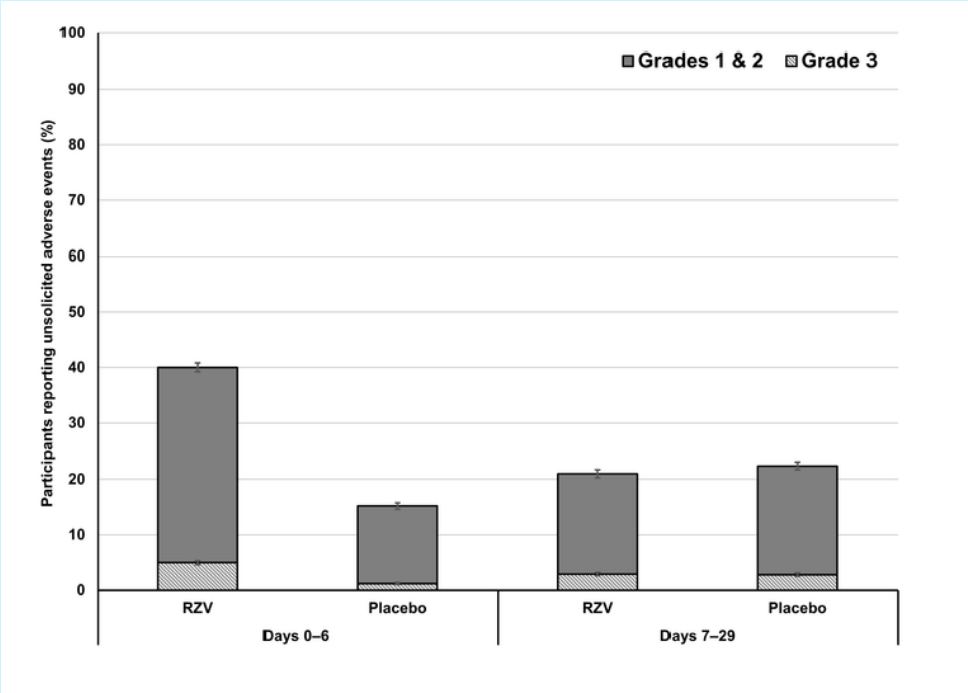
Table 2. Vaccine Efficacy against the First or Only Episode of Herpes Zoster Infection.*

Cohort and Age Group	HZ/su Group				Placebo Group				Vaccine Efficacy†
	No. of Participants	No. of Confirmed Cases	Cumulative Follow-up Period ‡ *person-yr*	Rate of Herpes Zoster *no./1000 person-yr*	No. of Participants	No. of Confirmed Cases	Cumulative Follow-up Period‡ *person-yr*	Rate of Herpes Zoster *no./1000 person-yr*	% (95% CI)
Modified vaccinated cohort									
All participants in cohort	7344	6	23,297.0	0.3	7415	210	23,170.5	9.1	97.2 (93.7–99.0)
50–59 yr	3492	3	11,161.3	0.3	3525	87	11,134.7	7.8	96.6 (89.6–99.3)
60–69 yr	2141	2	7,007.9	0.3	2166	75	6,952.7	10.8	97.4 (90.1–99.7)
70 yr or older	1711	1	5,127.9	0.2	1724	48	5,083.0	9.4	97.9 (87.9–100.0)
Total vaccinated cohort									
All participants in cohort	7698	9	25,584.5	0.4	7713	235	25,359.9	9.3	96.2 (92.7–98.3)
50–59 yr	3645	3	12,244.9	0.2	3644	95	12,162.5	7.8	96.9 (90.6–99.4)
60–69 yr	2244	5	7,674.1	0.7	2246	83	7,581.8	10.9	94.1 (85.6–98.1)
70 yr or older	1809	1	5,665.5	0.2	1823	57	5,615.6	10.2	98.3 (89.9–100.0)

Table 3. Adverse Events and Reactogenicity.*

Variable	HZ/su Group		Placebo Group	
	no. of participants/total no.	*% (95% CI)*	*no. of participants/total no.*	*% (95% CI)*
Reactogenicity subgroup	4460		4466	
Within 30 days after vaccination				
Unsolicited report of adverse event	1308	29.3 (28.0–30.7)	1226	27.5 (26.1–28.8)
Grade 3 unsolicited report of adverse event†	208	4.7 (4.1–5.3)	151	3.4 (2.9–4.0)
Within 7 days after vaccination				
Solicited or unsolicited report of adverse event	3765	84.4 (83.3–85.5)	1689	37.8 (36.4–39.3)
Grade 3 solicited or unsolicited report of adverse event†	760	17.0 (15.9–18.2)	145	3.2 (2.7–3.8)
Grade 3 solicited or unsolicited report of adverse event related to vaccination	694	15.6 (14.5–16.7)	83	1.9 (1.5–2.3)
Solicited report of injection-site reaction	3571/4382	81.5 (80.3–82.6)	522/4377	11.9 (11.0–12.9)
Pain	3464/4382	79.1 (77.8–80.2)	490/4377	11.2 (10.3–12.2)
Redness	1664/4382	38.0 (36.5–39.4)	59/4377	1.3 (1.0–1.7)
Swelling	1153/4382	26.3 (25.0–27.6)	46/4377	1.1 (0.8–1.4)
Grade 3 solicited report of injection-site reaction†	417/4382	9.5 (8.7–10.4)	16/4377	0.4 (0.2–0.6)
Solicited report of systemic reaction	2894/4375	66.1 (64.7–67.6)	1293/4378	29.5 (28.2–30.9)
Myalgia	2025/4375	46.3 (44.8–47.8)	530/4378	12.1 (11.2–13.1)
Fatigue	2008/4375	45.9 (44.4–47.4)	728/4378	16.6 (15.5–17.8)
Headache	1716/4375	39.2 (37.8–40.7)	700/4378	16.0 (14.9–17.1)
Shivering	1232/4375	28.2 (26.8–29.5)	259/4378	5.9 (5.2–6.7)
Fever	939/4375	21.5 (20.3–22.7)	132/4378	3.0 (2.5–3.6)
Gastrointestinal symptoms	788/4375	18.0 (16.9–19.2)	387/4378	8.8 (8.0–9.7)
Grade 3 solicited report of systemic reaction†	498/4375	11.4 (10.5–12.4)	106/4378	2.4 (2.0–2.9)

Safety profile of the adjuvanted recombinant Zoster vaccine: Pooled analysis from two large Randomized Phase III trials (IDWeek 2017; CID 2018, submitted)



N=14,465 RZV vs 14,660 placebo
No difference in SAEs, fatal AE or pIMD

What do we know about immunocompromised hosts?

Safety and immunogenicity of adjuvanted recombinant HZ vaccine in patients post-renal transplant (Zoster 041)

- Incidence of HZ 9X higher in SOT recipients
- Phase III RDBPCT; 2 doses of RZV 1-2 months apart; 4-18 months post transplant
- N= 264 (132 RZV, 132 Placebo)
- gE-specific humoral and cell-mediated immune responses higher in RZV than placebo recipients and persisted above pre-vaccination baseline 12M post-dose 2.
- Local AEs were reported more frequently by RZV than placebo recipients.
- Overall occurrences of renal function changes, rejections, unsolicited AEs, SAEs, and pIMDs were similar between groups.

Vink et al. IDWeek 2017, IDWeek 2018, CID 2018 (under review)

Efficacy of RZV inRenal Transplant Recipients: Suspected HZ

	RZV N=132	Placebo N=132
All (From dose 1)	3 (2.3%)	7 (5.3)
From dose 2	2 (1.5%)	6 (4.5%)

Immunogenicity and Safety of the Adjuvanted Recombinant Zoster Vaccine in Patients with Solid Tumors, Vaccinated Before or During Chemotherapy: A Randomized Trial

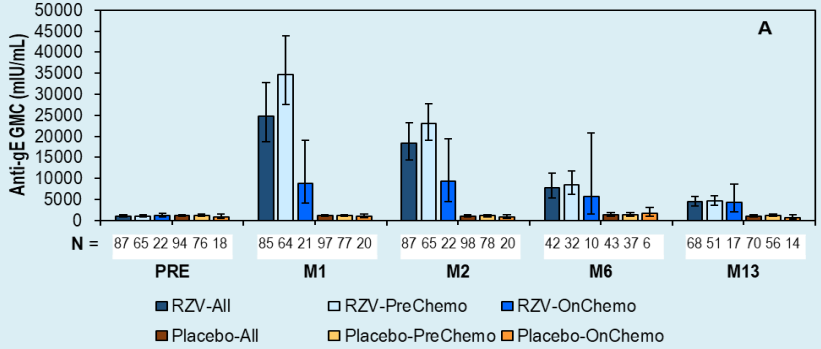
P Vink, I Delgado Mingorance, C Alonso, B Viqueira, K Jung, J Rodriguez Moreno, E Grande, D Gonzalez, S Lowndes, Javier Vazquez, H Kristeleit, D Farrugia, **S McNeil**, L Campora, E Di Paolo, M El Idrissi, O Godeaux, M López-Fauqued, B Salaun, T Heineman, and L Oostvogels, on behalf of the Zoster-028 study group*

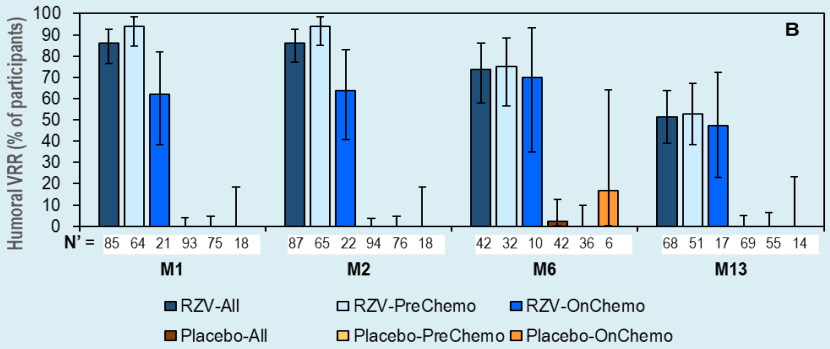
Vink et al. IDWeek 2017; Cancer 2018 (accepted)

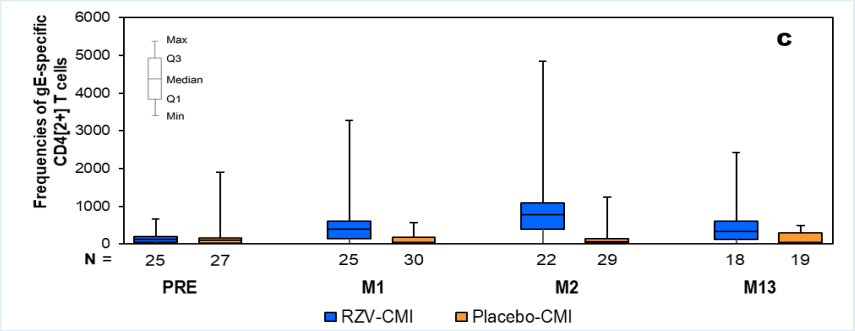
- Phase II/III, observer-blind, multicenter study (NCT01798056), patients with STs ≥18 YOA were randomized (1:1) to receive 2 doses of RZV or placebo 1–2 months (M) apart
- stratified (4:1) according to the timing of the first dose with respect to the start of a chemotherapy cycle: first vaccination at 8–30 days before the start or at the start (±1 day) of a chemotherapy cycle.

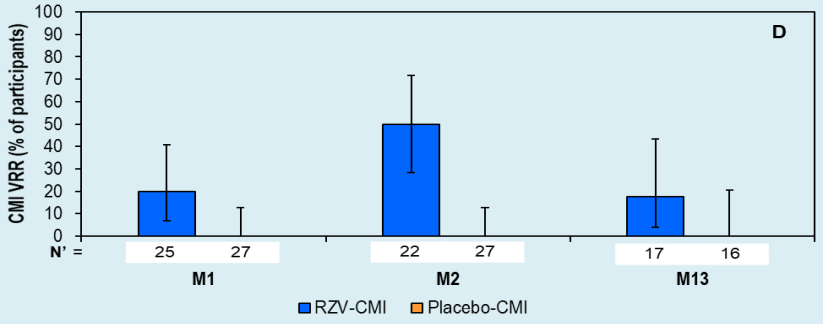
Humoral and cellular immune responses

(n=103/108 pre; 27/24 on)

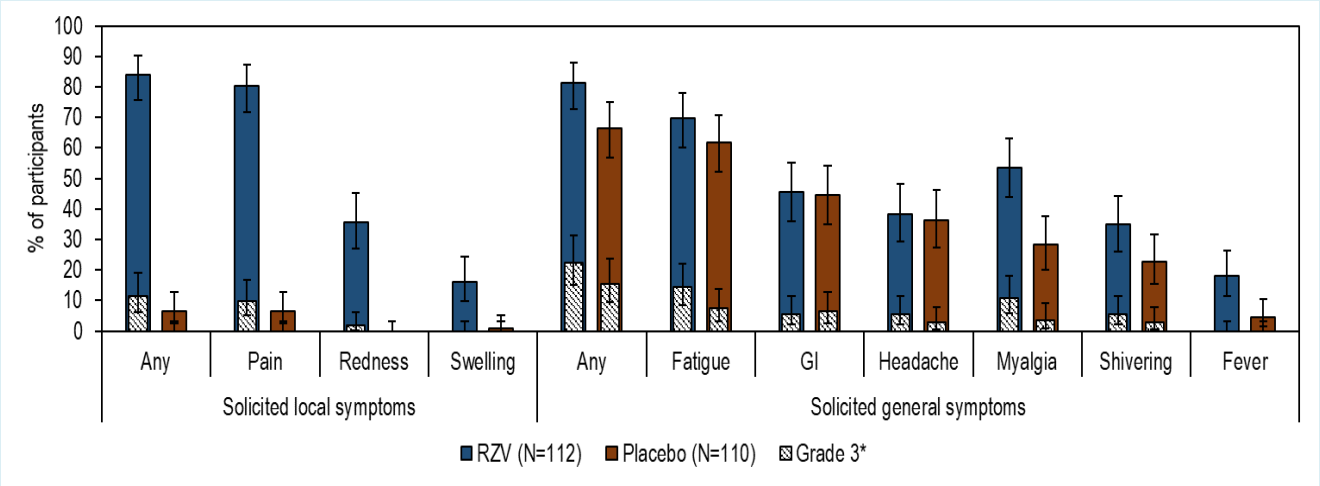








Reactogenicity

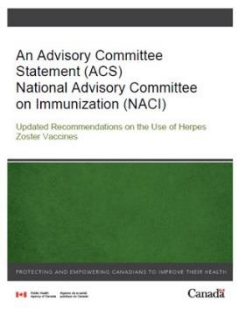


Conclusions

- RZV stimulates a humoral and cell-mediated immune response in patients with solid tumor malignancy if given prior to or at the start of chemotherapy
- RZV is safe and well-tolerated in this pop'n
- RZV may offer protection in this high-risk group

Conclusions

- Adjuvanted subunit vaccine demonstrates excellent efficacy in healthy adults of all ages
- Excellent immunogenicity in HIV/HSCT
- Efficacy in immunocompromised patients being evaluated
- May fill important gap for prevention of HZ in IC hosts
- Adverse event profile and 2 dose schedule may pose challenges for optimal uptake



NACI Recommendations (Aug 2018)

1. RZV should be offered to populations ≥50 years of age without contraindications. (Strong NACI Recommendation, Grade A evidence)

2. RZV should be offered to populations ≥ 50 years of age without contraindications who have previously been vaccinated with LZV. (Strong NACI Recommendation, Grade A Evidence)

1. Re-immunization with 2 doses of RZV may be considered at least one year after LZV (Discretionary NACI Recommendation, Grade I evidence)

NACI cont.

3. RZV should be offered to populations ≥ 50 years of age without contraindications who have had a previous episode of HZ. (Strong NACI Recommendation, Grade B Evidence)

1. Immunization with 2 doses of RZV may be considered at least one year after the HZ episode (Discretionary NACI Recommendation, Grade I evidence)

NACI cont.

4. LZV may be considered for immunocompetent populations ≥50 years of age without contraindications when RZV vaccine is contraindicated, unavailable or inaccessible. (Discretionary NACI Recommendation, Grade A evidence).

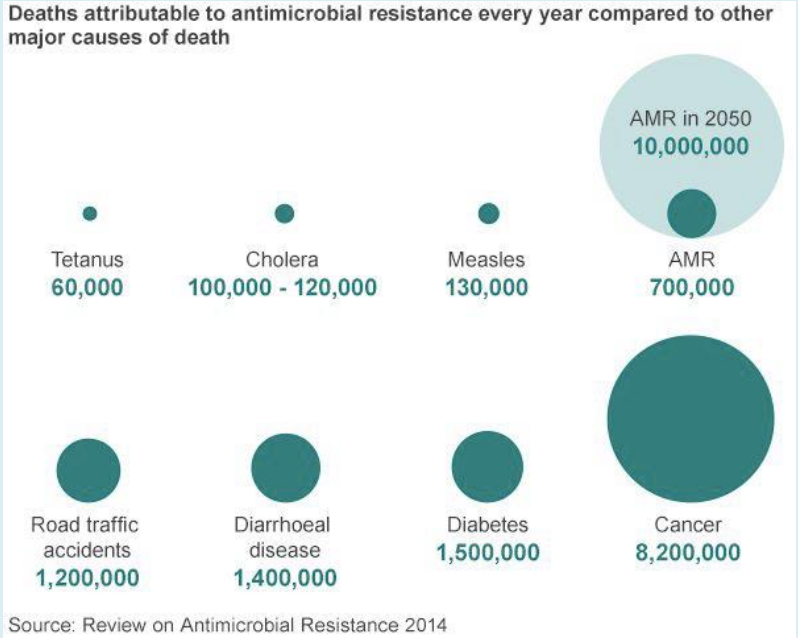
5. RZV (not LZV) may be considered for immunocompromised adults ≥50 years of age. (Discretionary NACI Recommendation, Grade I evidence). NACI will monitor results from ongoing trials in those who are immunocompromised and will reassess recommendations as evidence becomes available.

Vaccination and Herd Immunity in the Prevention of Antimicrobial Resistance

*Slides provided by Mark Loeb MD, MSc, FRCPC, McMaster University

RAND Europe: Burden of Antimicrobial Resistance

- Drug resistant infections will kill an extra 10 million people a year worldwide by 2050 - more than currently die from cancer



Approach to therapy in Infectious Diseases

- Practise is to begin with broader spectrum antibiotic or antibiotics, targeting the most likely pathogens
- Severity is important, coverage is rationally broadened for syndromes where failure to treat with effective therapy can lead to death
- Such initial therapy is “empiric”, that is, without knowledge of microbiology results
- The downside is empiric use that drives resistance
- Once a pathogen is identified and its susceptibility determined, therapy is narrowed to an effective agent

Our Diagnostic Tests are Limited

- Ideally, having point of care tests that distinguish resistant from susceptible pathogens
- Distinguish viral versus bacterial
- Identify specific pathogen
- Rapid answer, ideally within 1 hour

Caliendo AM et al, CID 2013; S139-70

World Health Organization

Why is vaccination important for addressing antibiotic resistance?

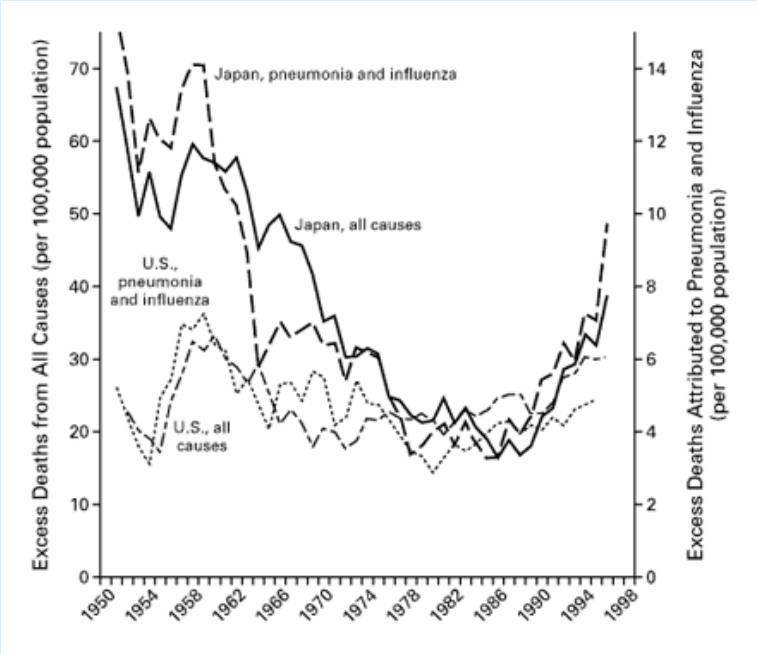
- Vaccinating humans and animals is a very effective way to stop them from getting infected and thereby preventing the need for antibiotics.
- Making better use of existing vaccines and developing new vaccines are important ways to tackle antibiotic resistance and reduce preventable illness and deaths.
- Vaccines against viruses, such as the flu, also have a role to play, because people often take antibiotics unnecessarily when they have symptoms such as fever that can be caused by a virus.

Herd Immunity/ Community Protection

"The resistance of a group to attack by a disease to which a large proportion of the members are immune, thus lessening the likelihood of a patient with a disease coming into contact with a susceptible individual"

Fox JP et al, Am J Epidemiol 1971; 94:179-189

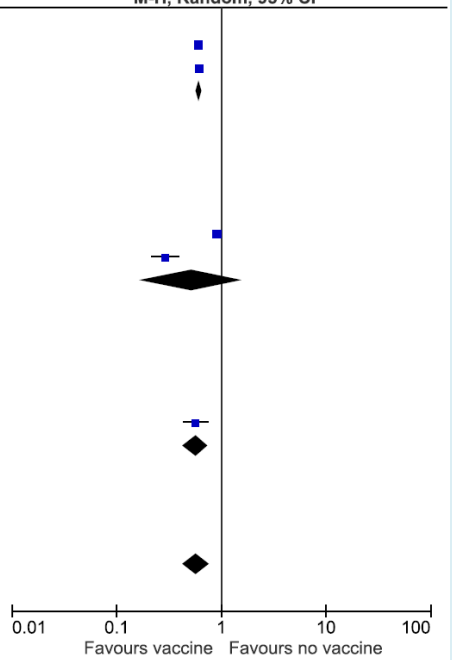
Influenza Vaccination of School children in Japan Reduction in Excess Pneumonia and Influenza Mortality Among Older Adults



Reichert T et al. NEJM 2001;344:889-96.

Meta-analysis of Observational Studies for Herd effect in Influenza

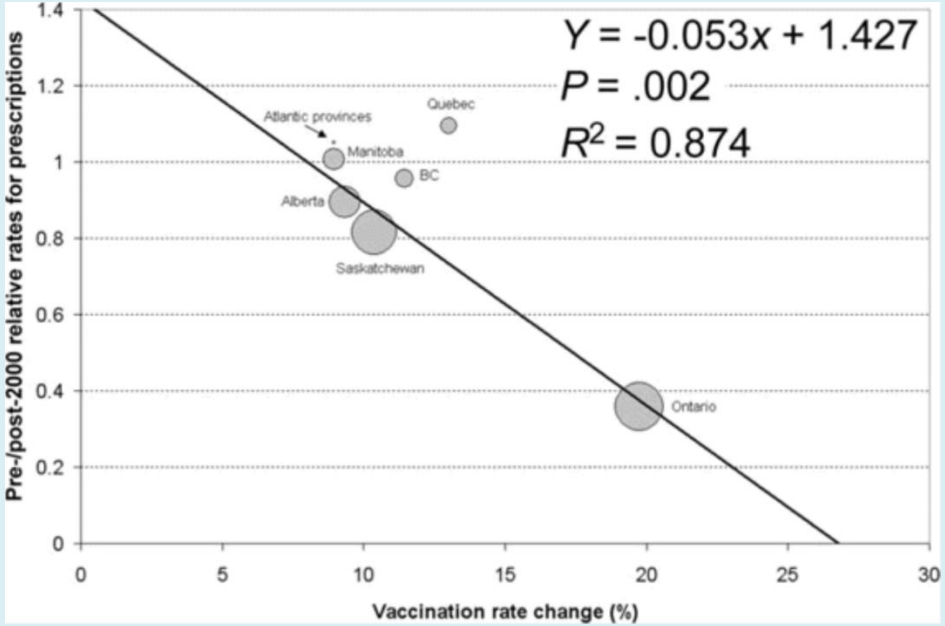
Study or Subgroup	Vaccine group Events	Total	Control group Events	Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
1.1.1 Household setting							
King 2006 (adult contacts)	979	3022	2429	5488	21.3%	0.60 [0.55, 0.66]	2006
King 2006 (children contacts)	1220	3022	2874	5488	21.3%	0.62 [0.56, 0.67]	2006
Subtotal (95% CI)		**6044**		**10976**	**42.5%**	**0.61 [0.57, 0.65]**	
Total events	2199		5303				
Heterogeneity: Tau² = 0.00; Chi² = 0.09, df = 1 (P = 0.76); I² = 0%							
Test for overall effect: Z = 15.00 (P < 0.00001)							
1.1.2 Community setting							
Piedra 2005	32306	161695	40823	188601	21.7%	0.90 [0.89, 0.92]	2005
Ghendon 2006	57	82051	183	76401	17.7%	0.29 [0.22, 0.39]	2006
Subtotal (95% CI)		**243746**		**265002**	**39.4%**	**0.52 [0.17, 1.58]**	
Total events	32363		41006				
Heterogeneity: Tau² = 0.64; Chi² = 56.10, df = 1 (P < 0.00001); I² = 98%							
Test for overall effect: Z = 1.16 (P = 0.25)							
1.1.3 School setting							
Kjos 2013	146	551	150	386	18.1%	0.57 [0.43, 0.75]	2013
Subtotal (95% CI)		**551**		**386**	**18.1%**	**0.57 [0.43, 0.75]**	
Total events	146		150				
Heterogeneity: Not applicable							
Test for overall effect: Z = 3.99 (P < 0.0001)							
Total (95% CI)		**250341**		**276364**	**100.0%**	**0.57 [0.43, 0.77]**	
Total events	34708		46459				
Heterogeneity: Tau² = 0.10; Chi² = 197.18, df = 4 (P < 0.00001); I² = 98%							
Test for overall effect: Z = 3.76 (P = 0.0002)							
Test for subgroup differences: Chi² = 0.33, df = 2 (P = 0.85), I² = 0%							



Reduction of Antibiotic Prescribing

- 30% reduction in antibiotic use in 2 RCTs of influenza vaccine in infants and children-
  - **RR 0.70, (95%CI: 0.59 to 0.83)**

Norhayati MN, Cochrane Syst Rev, 2017



From: **The Effect of Universal Influenza Immunization on Antibiotic Prescriptions: An Ecological Study**

Clin Infect Dis. 2009;49(5):750-756. doi:10.1086/605087

Major Mechanisms of Secondary Bacterial Infection following influenza

- Epithelial Cell damage
- Changes in Airway function
- Up regulation and exposure of receptors
- Alteration of Innate immunity
- Effects on the virus
- Enhancement of inflammation

McCullers J. Clin Micro Reviews 2006; 19:571-582
J Innate Immunity 2012
Sun K et al, Nature Medicine 2008

Summary

- Vaccination is an important strategy for reducing antimicrobial resistance
- Vaccination can lead to herd effect that indirectly prevents influenza and pneumococcal disease
- In so doing, this reduces infection, hospitalization, and antibiotic use

Acknowledgements

Thanks to Jan McElhaney for sharing her slides and wisdom. Thanks to Mark Loeb for sharing slides.
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Thank you!

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